# Social development in adolescence: brain and behavioural changes

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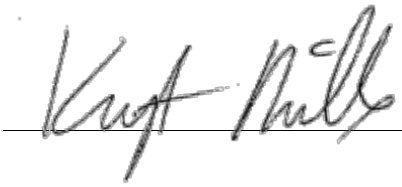
## Declaration

I, Kathryn Leeann Mills, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:  Date: 22 May 2015

Part of the work* presented in Chapters 1, 2, 4, 5, 6, 7 and 8 has been published in the following papers:

Blakemore S-J & Mills KL (2014). Is adolescence a sensitive period for socio-cultural processing? Annual Review of Psychology.

Mills KL & Tamnes CK (2014). Methods and considerations for longitudinal structural brain imaging analysis across development. Developmental Cognitive Neuroscience

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Mills KL, Goddings AL, Clasen LS, Giedd JN & Blakemore S-J (2014). The developmental mismatch in structural brain maturation during adolescence. Developmental Neuroscience.

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**The majority of the work presented in this thesis was conceptualised, conducted, and written by myself, with input from the co-authors of the published papers included. The work presented in this thesis differs from the published papers, as I have updated, edited, and extended the chapters where appropriate.*

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## Abstract

The period of life between puberty and adulthood, adolescence, has perplexed adults for millennia. Adolescence is marked by significant physical, cognitive, and social changes. Social lives become more complex during adolescence, and the teenage years are when we hone our skills at navigating the social world. The aim of my thesis was to examine brain development and social interactions during the period of adolescence.

I conducted three brain imaging experiments to investigate typical developmental trajectories of brain structure between childhood and adulthood. These three studies used a large longitudinal dataset and mixed-effects modelling in order to account for individual differences. My first study found evidence that intracranial volume continues to develop through the second decade, and describes the consequences of intracranial volume correction procedures on developmental studies. The second study provided evidence for the hypothesis that subcortical brain regions involved in processing affect and reward structurally mature before prefrontal cortical regions involved in cognitive control to varying degrees across individuals. The third study found evidence for continued structural development regions of the brain involved in understanding other people between late childhood to early adulthood. My behavioural experiment showed that keeping track of non-social information impacts the ability to navigate social interactions in adolescents and adults.

In addition to these four empirical studies, I conducted three reviews to synthesise and update our understanding of a) adolescence as a potential sensitive period for social learning, b) what longitudinal structural brain imaging studies can tell us about brain development, and c) the evidence for how using the Internet could impact brain development in adolescence.

Overall, my findings shed new light, and challenge current theories, on brain development and social cognition during adolescence.

# Table of Contents

## List of figures

## List of tables

## Abbreviations

| | |
|---|---|
| ATC | Anterior temporal cortex |
| AIC | Akaike information criterion |
| BA | Brodmann area |
| BOLD | Blood oxygenation level-dependent |
| CPB | Child Psychiatry Branch (NIMH) |
| CSF | Cerebro-spinal fluid |
| DHEA | Dehydroepiandrostenedione |
| dlPFC | Dorso-lateral prefrontal cortex |
| dmPFC | Dorso-medial prefrontal cortex |
| fMRI | Functional magnetic resonance imaging |
| ICV | Intracranial volume |
| mBA10 | Medial Brodmann Area 10 |
| mPFC | Medial prefrontal cortex |
| MRI | Magnetic resonance imaging |
| NAcc | Nucleus accumbens |
| NIMH | National Institute of Mental Health |
| OFC | Orbitofrontal cortex |
| PFC | Prefrontal cortex |
| pSTS | Posterior superior temporal sulcus |
| ROI | Region of interest |
| RT | Reaction time |
| STS | Superior temporal sulcus |
| TPJ | Temporo-parietal junction |
| vmPFC | Ventro-medial prefrontal cortex |
| vlPFC | Ventro-lateral prefrontal cortex |
| WM | Working memory |

# Chapter 1 Introduction

## 1.1 Background

Adolescence is often defined as the period between the onset of puberty and the achievement of relative self-sufficiency. Therefore the beginning of adolescence is largely defined by a biological event, whereas the end of adolescence is often defined socially. Recently, with the advent of brain imaging technologies, we have begun to understand changes occurring in the brain during this period of life. This introduction outlines i) the current research on social cognitive development in adolescence, and ii) our current knowledge of brain development through longitudinal investigations.

In the first part, I review research across psychology and neuroscience under the framework that adolescents' health and well-being are influenced through interacting with their social environment (Call et al., 2002). This framework addresses the social contextual factors and motivations that might influence behaviour during adolescence. I propose that social context and social acceptance play a pivotal role in adolescence, as they influence the majority of adolescent-typical behaviours. Based on my review of the literature, I hypothesise that adolescence is a period of heightened sensitivity and receptivity to social signals in the environment.

In the second part, I review several longitudinal magnetic resonance imaging (MRI) investigations of brain development in childhood and/or adolescence. I describe commonly used structural MRI measures, and integrate the results from several datasets to update our current understanding of brain development.

## 1.2 Adolescent behaviours and cognitive development

Human adolescence begins with the physical, cognitive, and social changes that occur with the onset of puberty. The adults that emerge from adolescence must be equipped to navigate the social complexities of their community. To understand and appreciate the changes occurring in adolescence, it is necessary to describe some of the changes occurring in the social environment, which is different from the child and adult social environments in many ways. For example, in many industrialised nations, the transition from primary to secondary school often occurs around the onset of puberty. This transition may place children into new environments with unfamiliar peers, in a different structure of learning, and at the bottom of the age hierarchy. Adolescents are also exposed to novel situations that they were unlikely to encounter as children, which might play a role in the increased novelty seeking seen in the transition from childhood to adolescence. In this section, I review the evidence for current and influential theories about adolescent-typical behaviours and cognitive development. I discuss developmental changes in: i) executive functions; ii) self-consciousness; iii) peer relations; and iv) risk taking; in relation to their probable impact on social cognition and behaviour during adolescence.

### 1.2.1 Executive functions

One of the most striking aspects of adolescent development is the increased capability for abstract thinking and problem solving (Demetriou, Christou, Spanoudis, & Platsidou, 2002). Cognitive control capabilities (i.e. executive functions) such as processing speed, voluntary response suppression, planning for the future, and working memory, continue to develop through adolescence (Luna,

Garver, Urban, Lazar, & Sweeney, 2004). The continued development of these capabilities permits more complex social interactions. Increases in processing speed allows for better temporal coordination, the ability to maintain and manipulate multiple items in working memory is helpful for tracking the mental states of others, and the ability to inhibit inappropriate responses and engage in purposeful actions are almost prerequisites for successful social interactions. Furthermore, the ability to consider the future consequences of actions continues to improve across adolescence (Crone & van der Molen, 2004), which might impact upon how adolescents interact in social situations. Both young adolescents (12 to 14 years) and older adolescents (16 to 18 years) showed heart rate slowing after erring on a task-switching task, which might indicate an increasing ability to monitor performance (Crone, Somsen, Zanolie, & Van der Molen, 2006). The ability to monitor one's performance in social situations likely affects the overall success of the interaction.

While adolescents perform many experimental tasks involving executive functions similarly to adults, this is largely true only for tasks carried out in "cold" (non-emotional or non-motivational) contexts (Blakemore & Robbins, 2012). There is evidence that adolescents and adults behave differently in experimental tasks carried out in "hot" contexts, such as tasks that are high in emotional salience. For example, successful emotion regulation in early adolescence is impacted by an adolescent's sensitivity to rejection as well as situational factors of the emotional stimuli. Compared with older adolescents and adults (14 to 23 years), young adolescents (10 to 13 years) found it harder to regulate their emotions when presented with social affective stimuli compared to nonsocial affective stimuli (Silvers et al., 2012).

Further, developmental neuroimaging studies show correlations between the protracted development of the neural networks and the maturation of executive functions during adolescence. The ability to suppress reflexive, or context-inappropriate, behaviour is associated with the increased functional integration of a network of cortical and subcortical brain regions between childhood and adulthood (Luna et al., 2001). Improvements in the ability to manipulate multiple items in mind is associated with increased recruitment of areas in the prefrontal and parietal cortices between childhood and adolescence (Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006). Both structural and functional changes in the prefrontal cortex and anterior insula relate to developmental changes in the ability to assess similarities between items that vary along multiple dimensions (relational reasoning) (Dumontheil, Houlton, Christoff, & Blakemore, 2010). Developmental neuroimaging studies suggest that distinct neural systems develop at different rates across childhood and adolescence, and that age-related changes in regions involved in feedback processing may underlie behavioural differences in flexible performance adjustment (Crone, Zanolie, Van Leijenhorst, Westenberg, & Rombouts, 2008). A qualitative shift in neural recruitment during feedback-based learning is seen in early adolescence, possibly reflecting the increasing influence of negative feedback on behavioural adjustment (van Duijvenvoorde, Zanolie, Rombouts, Raijmakers, & Crone, 2008).

### 1.2.2 Self-consciousness

The increasing capacity to hold in mind abstract concepts between childhood and adolescence also coincides with an increasing ability to reflect upon one's self (Pfeifer & Peake, 2012; Sebastian, Burnett, & Blakemore, 2008). One's role in,

and relationship to, the world becomes more apparent in adolescence – historically defined as a period of identity formation and development (Erikson, 1968, 1980). Longitudinal studies using self-report measures have provided conflicting evidence regarding the development of self-consciousness in adolescence. These studies used the Self-Consciousness Scale (Fenigstein, Scheier, & Buss, 1975), which assesses an individual's tendency to engage in two kinds of self-conscious behaviour: *private self-consciousness*, the tendency to pay attention to private aspects of the self such as motives and feelings; *public self-consciousness*, the tendency to be aware of and concerned with one's public self-aspects such as physical appearance. An early longitudinal study of adolescents aged 14–17 years found no change in private or public self-consciousness across a 2-year testing period (Davis & Franzoi, 1991). A more recent longitudinal study covering a larger age range (13–18 years), and longer testing period (4 years) found evidence for a decrease in public self-consciousness, and an increase in private self-consciousness, across this age period (Rankin, Lane, Gibbons, & Gerrard, 2004). Despite the observed decrease in public self-consciousness, public self-consciousness was consistently reported as greater than private self-consciousness between ages 13 and 18 years (Rankin et al., 2004). Private self-consciousness in adolescents is similar to levels reported in adults, whereas public self-consciousness continues to decrease between adolescence and adulthood (Frankenberger, 2000).

Early theories about adolescent self-consciousness framed this developmental change as "egocentrism" (Elkind, 1967). Elkind posited that young adolescents, as compared to children and older adolescents (age 15–18 years), were less able to differentiate between the cognitive concerns of others and those of the self, and

that adolescents were susceptible to two mental constructs: the *imaginary audience* and *personal fable* (1967). The first construct referred to the idea that adolescents are so preoccupied with how others perceive them that they believe that others are judging them in social situations when they in fact are not (that the audience is indeed imaginary). The second construct, the personal fable, referred to the idea that adolescents believe their experiences to be unique, of universal importance, and that death will happen to others but not to oneself. While the theories presented in Elkind's 1967 article continue to persist in today's textbooks and public rhetoric, as well as to provide the motivation for modern experiments on adolescent development, there has been little empirical support for them (Vartanian, 2000). A large study (n=1470) using hypothetical peer group conversations found no evidence for the idea that adolescents believe others are attentive to and critical of their every move (Vartanian, 2001). And in contrast to the idea that adolescents construct an imaginary audience because they lack the ability to differentiate between their personal concerns and the concerns of others, one study found evidence that adolescents are preoccupied with the opinions of others because of the relevance of others' opinions to their own identity development and social standing (Bell & Bromnick, 2003). The authors of this study suggest that there is nothing imaginary about the audience that adolescents imagine when trying to understand how others perceive them. It appears that self-consciousness in adolescence is fundamental to identity development, as adolescents become less self-conscious as they become more certain of their identity (Adams, Abraham, & Markstrom, 1987). Behavioural studies have found that introspective awareness of one's performance on a perceptual task improves across adolescence (Weil et al., 2013). Increases in self-awareness during

adolescence might have implications for how adolescents integrate their own self-judgments with peer evaluations, which I discuss in the following section.

### 1.2.3 Peer relations

The transition between childhood and adolescence is typically considered a period of "social reorientation" with adolescents spending more time with peers and less time with their family than they did as children (Nelson, Leibenluft, McClure, & Pine, 2005). Despite this popular theory, which provides the basis for many cognitive neuroscience studies on peer influence and social development in adolescence, empirical investigations on how adolescents spend their time paint a more complex picture. To begin, the earliest and most highly cited studies in support of this theory were either based on small samples (n=75; Csikszentmihalyi & Larson, 1986), or consisted of white, suburban, working-class and middle-class, American youth (Larson & Richards, 1989, 1991; Larson, Richards, Moneta, Holmbeck, & Duckett, 1996). Using experience-sample methods, these studies found that time spent with their parents decreased by half between ages 9–15 years in white suburban youth (n=483) (Larson & Richards, 1991). In this sample, time spent alone increased for both male and female participants, whereas time spent with peers increased during this age range only for the female participants. While these studies are often discussed in terms of shifting external influences on adolescents' behaviour, the decreased quantity of time spent with family members was reported by the adolescents in this sample as *qualitatively better* than interactions in late childhood (e.g., more dyadic and direct), and there was no change in the amount of time spent actually talking to family members across this age period (Larson et al., 1996). While commonly overlooked in the field of developmental neuroscience, it is imperative to consider

the substantial variability that exists between cultures in how children and adolescents spend their time. For example, a study of urban African-American youth (n=253) reported no change in the amount of time spent with family across ages 10–15 years, and reported no increase in time spent alone or with friends (Larson, Richards, Sims, & Dworkin, 2001). Further, studies of Japanese, Korean and middle-class Indian youth have found that time with family actually *increased* through adolescence (Larson & Verma, 1999).

Despite conflicting reports as to whether children begin to spend more time with peers as they transition into adolescence, there is evidence that the evaluations of peers become more important during this time. Adolescents aged 13 to 17 years reported that peer evaluations affect their feelings of social or personal worth and that peer rejection indicates their unworthiness as an individual (O'Brien & Bierman, 1988). Although both the adolescents and children aged 10 to 13 years similarly felt that peers provided companionship, stimulation, and support, the younger group did not indicate that peer acceptance impacted self-evaluation. The authors suggest that increasing abilities to form abstract representations, as well as increasing motivation for peer acceptance, might account for the influence of peers on self-evaluations in adolescence. These self-reported accounts of the importance of peer acceptance are supported by the results of a behavioural study investigating the effects of social exclusion in the lab. After being excluded by other players in an online game called Cyberball, young and mid-adolescents (11–16 years) reported lowered overall mood, and young adolescents (11–14 years) reported higher state anxiety, compared with adults (Sebastian, Viding, Williams, & Blakemore, 2010). Thus, it appears that the desire to be accepted by one's

peers, and avoidance of social rejection, is particularly acute in adolescence and might drive adolescent behaviour (Figure 1.1).

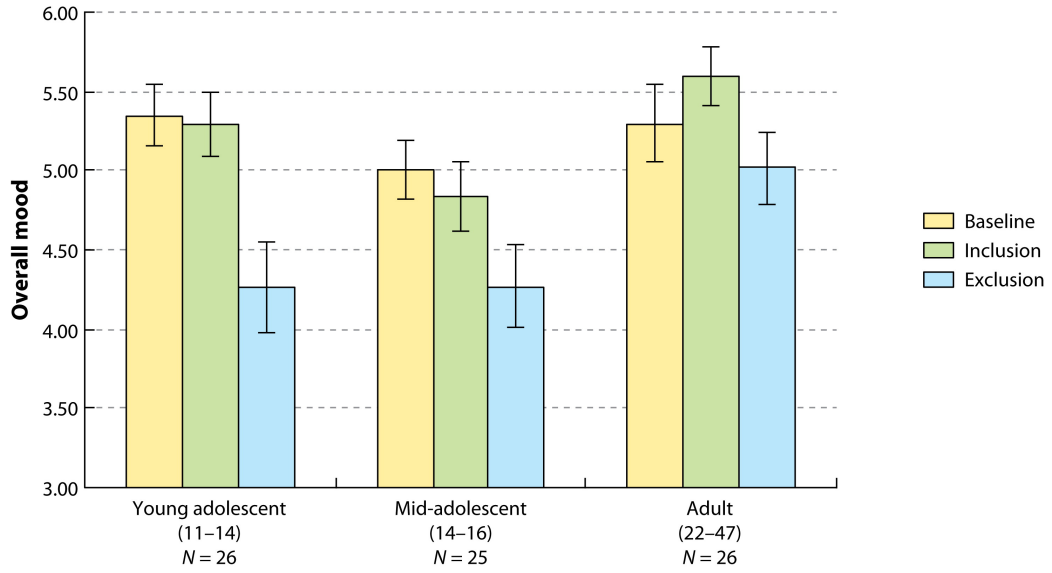


**Figure 1.1. Consequences of social exclusion on mood.** Adolescents are hypersensitive to the negative consequences of social exclusion. In this study, young adolescents (11–14 years), mid-adolescents (14–16 years), and adults (22–47 years) first completed baseline measures of mood. They then played the Cyberball online ball game and were either included or excluded by the other players in the game. After each run (inclusion and exclusion), participants completed measures of mood again. The graph shows overall mood ratings for each group under each condition. Mood was lowered by the social exclusion condition, compared with baseline and inclusion, particularly strongly in the two adolescent groups. Figure adapted from Sebastian et al. (2010), and published in Blakemore & Mills, 2014.

### 1.2.4 Risk taking

Seeking experiences outside those offered in the immediate environment is a typical, and necessary, aspect of human development. In many societies, adolescence is a time of increasing autonomy, here defined as self-governance or agency – the ability to engage in self-directed behaviour (Beyers, Goossens, Vansant, & Moors, 2003; Ryan & Lynch, 1989). This increased capacity to engage in self-directed behaviours is associated largely with positive outcomes and achievement of developmental milestones (Eccles, Early, Fraser, Belansky, & McCarthy, 1997; Walls & Little, 2005). However, adolescence is stereotypically

considered a time of increased risk taking and sensation seeking (Steinberg, 2008). This intuitive theory has played a fundamental role in the formation of many studies of adolescent behaviour – especially neuroscience studies aimed at understanding the neural basis of this behavioural change. However, the types of risks commonly attributed to the period of adolescence are health risks, such as drug use, reckless driving, and unsafe sexual practices (Kann et al., 2014). While public health surveys confirm an increase in these behaviours between childhood and adolescence, there is no evidence that these behaviours actually peak in the teenage years. Instead, it appears that individuals that engage in unhealthy practices during their teenage years are risking the chance of adopting a method of navigating the world that will persist into adulthood (Kann et al., 2014). Further, to define risk taking with behaviours that children are unable (or typically do not have the opportunity) to engage in, one cannot accurately assess a change in behaviour between childhood and adolescence. Therefore, this section will focus on studies that investigate changes in decision making using methods that can be adequately assessed between childhood and adulthood.

Gambling tasks are one kind of task that can be used to assess how children, adolescents, and adults perceive and evaluate risky decisions. One study using a gambling task found that children and adolescents show adult levels of probability estimation and reward evaluation (Van Leijenhorst, Westenberg, & Crone, 2008). This suggests that adolescents are able to accurately evaluate the consequences of engaging in risky behaviours. Further, when asked in a laboratory setting to estimate the risks of negative outcomes to some risky behaviours, adolescents actually overestimate risks (Reyna & Farley, 2006). However, adolescents also rate the potential reward to be gained as very high, which may make the perceived

benefits outweigh the perceived risk (Reyna & Farley, 2006). Social and contextual cues can bias the way adolescents perceive the risk involved in certain behaviours (Reyna, 2008; Reyna & Adam, 2003; Reyna & Farley, 2006). Although risky decision making during adolescence is often framed as maladaptive and unavoidable, this perspective leaves out many key features of risky decision making, including the fact that the outcome can be positive and that some risky decision making is necessary in development and throughout life. A recent report highlights the benefits of asking "What's in it for the adolescent?" when studying risky behaviour and risky decision making in adolescence (B. J. Ellis et al., 2012). As many rewards gained by risky behaviours are social in nature, such as peer acceptance or the avoidance of social exclusion, social rewards are likely a potential major driver of risky behaviour – particularly during adolescence, when social acceptance is especially important (Crone & Dahl, 2012; Pfeifer & Allen, 2012).

Knowing that adolescents can feel differently to adults in social situations can help us understand how teenagers make decisions. Our actions, and the ways in which we choose to behave, are the result of a constant stream of decisions we are making. To make these decisions, we have to take all the information we have that is relevant and weigh up whether it is a good idea to act or not. This decision-making process can be viewed as a kind of see-saw (see Figure 1.2). All of the reasons in favor of doing an action – the positive outcomes – are placed on the "Yes" side of the see-saw, while the negative outcomes are placed on the "No" side. Older children and adolescents can perceive just as well as adults whether something good or bad is likely to happen as a result of an action, a process called risk perception (Van Leijenhorst et al., 2008). This decides which side of the see-

saw the outcome goes on. One thing that may differ between adolescents and adults is how much value they place on the good and bad outcomes, or how "heavy" each of the outcomes is on the seesaw. Adolescents tend to rate potential rewards as very high, which may make the perceived benefits (good outcomes) outweigh the perceived risk (bad outcomes).

There are many outcomes of a decision. While some outcomes of risky decisions are clearly positive or negative and remain relatively stable (e.g., serious health risks from smoking), the value of other outcomes of a decision might vary depending on the social environment. For example, even though we understand the extensive health risks of smoking, the social outcomes of smoking are variable. Socially, smoking can lead to peer acceptance and popularity, but can also lead to social stigma and disapproval, depending on the attitudes and opinions of your group of friends and your family (see Figure 1.2). Social outcomes vary between individuals and can be the reason that the decision-making see-saw tips one way or another, changing the decisions we make and the way we act in different socials contexts.

The see-saw model can help explain why different people make different choices by highlighting the value of social outcomes in decision making. These social outcomes are thought to be particularly important in adolescence. Using this model might make it easier to understand why teenagers (and children and adults) make risky decisions.

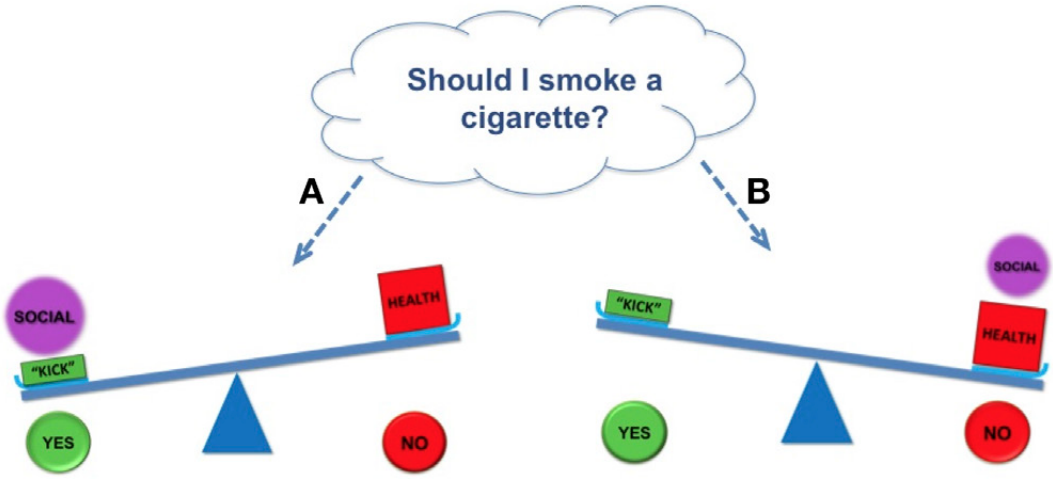


**Figure 1.2. Schematic "see-saw" model of some of the factors that influence certain risky decisions.** Every time we make a decision, we weigh up the good and bad outcomes. For example, when thinking "Should I smoke a cigarette?" we consider bad outcomes like health risks, but might also think that smoking gives us a positive feeling ("kick"). We also consider the social outcomes of our decisions. In this example, our friends and family might be upset or disapprove of our smoking, so that becomes a negative outcome, and we choose "No" (Option B). Alternatively, we might think that smoking will make us popular, a positive outcome, and we choose "Yes" (Option A).

## 1.3 Social cognitive development

Social cognition refers to the ability to make sense of the world through processing signals generated by members of the same species (C. D. Frith, 2008). Social cognitive processes include basic perceptual processes such as face processing (Farroni et al., 2005), biological motion detection (Pelphrey & Carter, 2008), and joint attention (Carpenter, Nagell, & Tomasello, 1998). From infancy, humans display signs of social cognition (Kovács, Téglás, & Endress, 2010; Striano & Reid, 2006). Other social cognitive processes are more complex, such as understanding others' mental states (Blakemore, den Ouden, Choudhury, & Frith, 2007), social emotional processing (Burnett, Bird, Moll, Frith, & Blakemore, 2009; Goddings, Burnett Heyes, Bird, Viner, & Blakemore, 2012), and negotiating complex interpersonal decisions (Crone, 2013). Recent neuroimaging and behavioural studies have shown that these skills continue to develop past childhood and throughout adolescence.

Until recently, there was a shortage of studies looking into social cognitive abilities after childhood, as it was generally assumed that these abilities were already mature by mid-childhood in typically developing children. Most paradigms have been designed to investigate social cognition (in particular, theory of mind) in young children and result in ceiling effects after mid-childhood (Apperly, 2010).

One of the first studies to investigate neurotypical changes in social cognitive behaviour in adolescence showed the ability to integrate the perspectives and intentions of others when making fairness considerations continues to improve (Güroğlu, van den Bos, & Crone, 2009). The authors of this study suggested that the rewarding nature of peer relationships during adolescence could affect social decision-making processes. Another study demonstrated that online social cognitive skills improve across adolescence (Dumontheil, Apperly, & Blakemore, 2010). Participants aged 7 to 27 years were tested on their ability to take the perspective of another person when making decisions. To test online social cognition, the authors adapted a referential communication task in which participants are instructed to move objects around a set of shelves by a director, who cannot see some of the objects that the participant can see. Adults frequently make mistakes in this type of trial, in which the participant needs to take account of the director's perspective in order to guide decisions (Keysar, Barr, Balin, & Brauner, 2000; Keysar, Lin, & Barr, 2003). As an added control, Dumontheil et al. (2010) included a condition in which the director is gone and participants have to follow a non-social rule ("ignore objects with a grey background") when following the (otherwise) same instructions as in the director condition. Although

accuracy improved until mid-adolescence in both conditions, accuracy in the director condition continued to improve after mid-adolescence (see Figure 1.3). This suggests that the ability to use another's perspective to guide decisions continues to develop beyond the establishment of abilities recruited in the control condition (e.g., working memory, response inhibition). This improvement may be due to increased motivation to take account of another's perspective as well as improved integration of social cognition and cognitive control systems (Dumontheil, Apperly, et al., 2010).

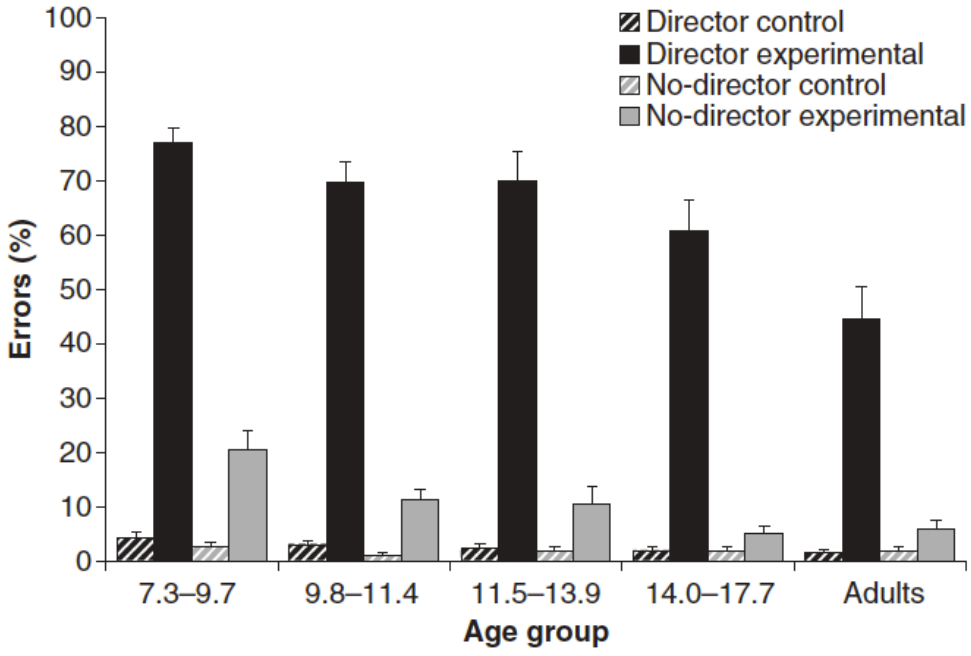


**Figure 1.3. Continued development of perspective taking between adolescence and adulthood.** These graphs show the average percentage errors (mean + SE) in the Director and No Director conditions for each age group. The experimental trials for the Director condition required participants to take account of the director's perspective, whereas participants had to follow the non-social rule of ignoring all objects in slots with a grey background for experimental trials in the No Director condition. Figure from Dumontheil et al. 2010.

## 1.4 The Social Brain Network

It has been proposed that social cognition has been so fundamental to the survival and reproductive fitness of various primate species that primate brains include

regions specialised for social cognitive processes (Brothers, 2002; Rushworth, Mars, & Sallet, 2013). Although this idea remains contentious, there exists a network of brain regions consistently involved in social cognitive processes (Adolphs, 2009; C. D. Frith, 2007). Mentalising, the process of mental state attribution, has been associated with a network of brain regions including the dorsal medial prefrontal cortex (dmPFC), temporoparietal junction (TPJ), posterior superior temporal sulcus (pSTS), and anterior temporal cortex (ATC) (Figure 1.4). Together, this set of regions is sometimes called the social brain network. The mentalising tasks that recruit these regions have used a variety of stimuli, such as animated shapes (Castelli, Happé, Frith, & Frith, 2000), cartoon stories (Brunet, Sarfati, Hardy-Baylé, & Decety, 2000; Gallagher et al., 2000), and written stories (Fletcher et al., 1995) designed to elicit the representation of mental states. Although the coactivation of these regions has been demonstrated in many social cognitive neuroimaging experiments, the individual contributions of these anatomically distinct regions to social cognitive processes are debated.

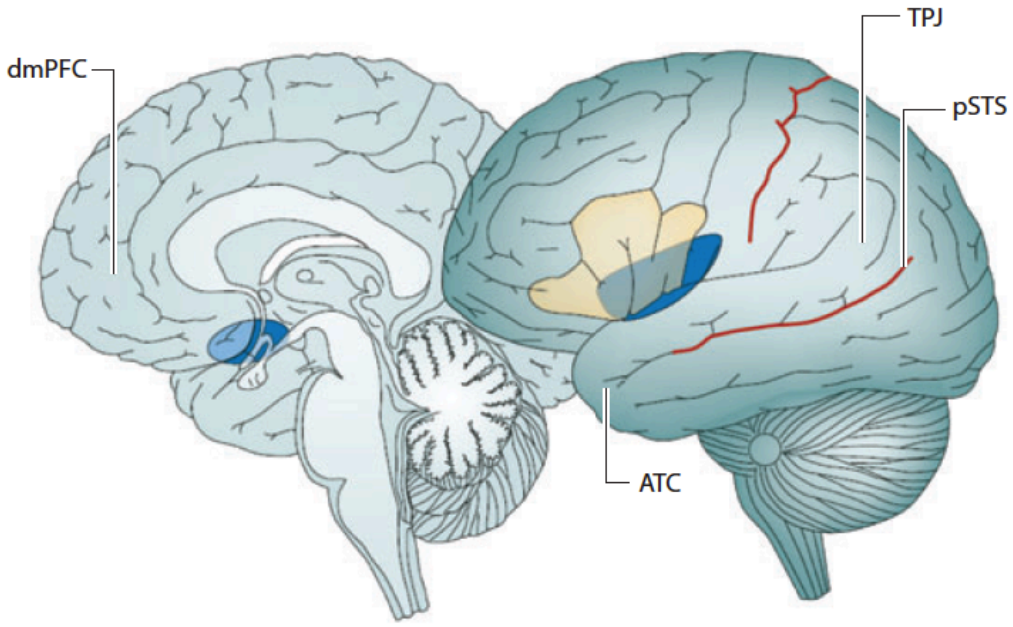


**Figure 1.4. The mentalising brain network: areas of the brain that may be sensitive to social cognitive processes necessary to navigate the adolescent social environment.** Regions on the lateral surface of the brain that are involved in social

cognition include the dorsal medial prefrontal cortex (dmPFC) and temporoparietal junction (TPJ), which are involved in thinking about mental states; the posterior superior temporal sulcus (pSTS), which is involved in observing faces and biological motion; and anterior temporal cortex (ATC), which is involved in applying social knowledge. Adapted from Blakemore (2008).

Electrophysiological and functional magnetic resonance imaging (fMRI) studies consistently report the involvement of the pSTS in the perception of biological motion and eye gaze (Puce & Perrett, 2003) and in grasping the intentionality and appropriateness of biological motion (Pelphrey, Morris, & McCarthy, 2004). It may be that the pSTS is involved in decoding complex social gestures conveyed through eye gaze and body movement. The TPJ, while in close anatomical proximity to the pSTS, is involved in different aspects of social cognition. It is suggested that the TPJ is activated specifically in situations when one is inferring the mental states of others rather than just information known about another (Saxe & Kanwisher, 2003; Saxe, Whitfield-Gabrieli, Scholz, & Pelphrey, 2009). In contrast, dmPFC is activated in multiple conditions: when inferring the mental states of others, when reflecting on knowledge of another's traits, and when reflecting on the traits of oneself (C. D. Frith, 2007). Frith (2007) has proposed that the underlying similarity between tasks that activate the dmPFC is their involvement in handling communicative intentions, which requires a second-order representation of mental state, whether our own or another's. A combination of lesion, nonhuman primate, and fMRI studies has prompted researchers to theorise the involvement of the ATC in applying social knowledge (Olson, McCoy, Klobusicky, & Ross, 2013) and processing social scripts (C. D. Frith, 2007; U. Frith & Frith, 2003).

Some of the strongest evidence linking areas of the mentalising brain network to adaptations to the social environment comes from primate studies. In macaques,

the size of an individual's social group is associated with both the structure and function of homologous brain areas involved in social cognition (Sallet et al., 2011). Macaques housed in more complex social environments had greater grey matter volume in the temporal cortex and rostral prefrontal cortex, and higher-ranking male macaques had greater grey matter volume in similar regions after controlling for network size, weight, and age (Sallet et al., 2011). These studies support the idea of the existence of a mentalising brain network as well as the idea that this network exists in nonhuman primates (Rushworth et al., 2013).

## 1.5 Functional development of the social brain network in adolescence

A number of fMRI studies show functional changes across adolescence in the brain networks associated with social cognition, including face processing, mentalising, peer evaluation, and peer influence. I discuss these studies below.

### 1.5.1 Face processing

Understanding the mental states of others by processing facial expressions is a crucial skill and is one that continues to develop across adolescence (McGivern, Andersen, Byrd, Mutter, & Reilly, 2002). Recruitment of the prefrontal cortex during face-processing tasks increases between childhood and adolescence and then decreases between adolescence and adulthood. Brain systems supporting detection and interpretation of communicative signals from face processing also show age-related changes from childhood to adulthood, perhaps due to changing cognitive strategies (Cohen Kadosh, Johnson, Dick, Cohen Kadosh, & Blakemore, 2012; Cohen Kadosh, Johnson, Henson, Dick, & Blakemore, 2012).

Recent longitudinal neuroimaging studies are beginning to provide evidence of changes in neural responses to social stimuli such as faces between childhood and adolescence. As participants transitioned from late childhood (age 10 years) to adolescence (age 13 years), they showed greater neural activity in the ventral striatum and ventromedial PFC while looking at facial displays (Pfeifer et al., 2011). The ATC was the only area to show a longitudinal change in preference for emotional facial displays. This study correlated longitudinal changes in ventral striatal activity with decreasing susceptibility (i.e., increasing resistance) to peer influence, demonstrating that heightened subcortical reactivity in socioemotional situations might indicate better emotion-regulation capacities (Pfeifer et al., 2011). In addition, pubertal status during early adolescence was related to increased neural recruitment of the amygdala, hippocampus, and ATC when participants looked at affective facial stimuli (i.e., happy, sad, angry faces) (Moore et al., 2012).

### 1.5.2 Mentalising

Many fMRI studies that use mentalising report decreases in dmPFC recruitment between adolescence and adulthood (reviewed in Blakemore 2008, 2012; see Figure 1.5). These studies have used a variety of tasks that require mental state attribution, such as understanding irony (Wang, Lee, Sigman, & Dapretto, 2006), thinking about social emotions such as guilt (Burnett et al., 2009), understanding intentions (Blakemore et al., 2007), understanding emotions from photographs of eyes (Gunther Moor et al., 2012), and thinking about the preferences and dispositions of oneself or a fictitious story character (Pfeifer et al., 2009). In some studies, higher activity in more posterior regions, such as the pSTS/TPJ (Blakemore et al., 2007), and in the ATC (Burnett et al., 2009), was observed in

adults as compared to adolescents. These changes in functional recruitment have been hypothesised to reflect changes in neurocognitive strategy and/or neuroanatomy (Blakemore, 2008).

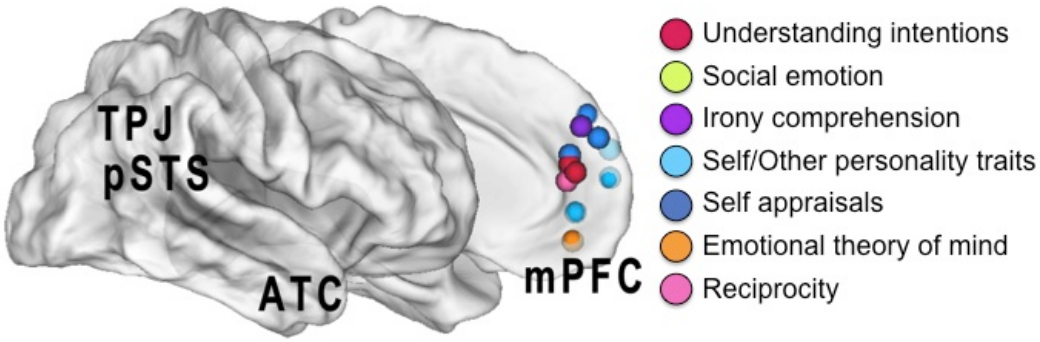


**Figure 1.5. Adolescents recruit the medial prefrontal cortex more than adults during mentalising tasks.** The mentalising tasks ranged from thinking about intentions, understanding irony, thinking about scenarios that involve social emotions, thinking about whether character traits describe oneself or another familiar other, and deciding on whether to reciprocate in a dual-player task. Adapted from Blakemore (2008).

In an adapted version of the Director task (Apperly et al., 2010a; Dumontheil, Apperly, et al., 2010), areas of the mentalising brain network were engaged when participants had to use social cues to select an appropriate action in a communicative context (Dumontheil, Hillebrandt, Apperly, & Blakemore, 2012). Although both adults and adolescents recruited the dmPFC when the social cues were needed to accurately perform the task, adolescents also recruited the dmPFC when social cues were not needed. The authors suggest that this engagement of the dmPFC in social conditions, even when social signals are irrelevant, may reflect the use of brain regions involved in mentalising even when they are not necessary during adolescence.

Adolescents also show developmental changes in sensitivity to the perspectives of others. In an fMRI study, young adolescents (12 to 14 years), older adolescents

(15 to 17 years), and emerging adults (18 to 22 years) completed a social exchange game in which participants were the second player in an investment game (van den Bos, van Dijk, Westenberg, Rombouts, & Crone, 2011). These participants were first given an amount of money by an anonymous first player, which they could divide equally between themselves and the first player (reciprocate) or keep most for themselves (defect). Participants' ability to understand the intentions of the first player was also measured by comparing trials on which the first player stood to lose a large amount of money by trusting the second player with trials where the first player stood to lose a relatively small amount of money. Older adolescents and emerging adults were more likely to reciprocate when the first player stood to lose more money, whereas the younger adolescents did not differentiate, supporting the idea that the ability to understand the intentions of others increases into adulthood. The recruitment of the left TPJ when participants were shown that the first player trusted them increased with age, and this level of activation correlated with participants' sensitivity to the first player's intentions. All participants showed greater recruitment in the dmPFC when making self-oriented choices (defecting), but only young adolescents engaged this region when making reciprocal choices. This heightened activation in the dmPFC for reciprocal choices decreased between early and late adolescence and remained stable into early adulthood (van den Bos et al., 2011).

### 1.5.3 Social emotion

Social emotions – such as guilt, embarrassment, shame, and pride – require representing another's mental state, whereas basic emotions such as fear and disgust do not. Because adolescence is a period of increased sensitivity to peer evaluation, there may be changes in how social emotions are processed. One

fMRI study investigated changes in neural recruitment during a social emotional task between adolescence (11 to 18 years) and adulthood (23 to 32 years) (Burnett et al., 2009). Participants were instructed to read sentences describing social or basic emotion scenarios. Adolescents recruited the dmPFC more than adults when reading social emotional sentences relative to basic emotion sentences. In contrast, adults recruited the left ATC more than did adolescents when reading social emotional sentences relative to basic emotion sentences (Burnett et al., 2009).

A more recent study investigated the influence of puberty on social emotion processing in adolescence (Goddings et al., 2012). In a sample of 42 female adolescents (11 to 13 years), levels of pubertal hormones (testosterone, oestradiol, and dehydroepiandrosterone (DHEA)) were related to ATC recruitment during social emotional processing. Whereas activity in the left ATC was positively correlated with hormone levels (irrespective of age), activity in the dmPFC was negatively correlated with chronological age (irrespective of hormone levels), providing evidence for a dissociation between puberty- and age-related changes in neural function during adolescence (Goddings et al., 2012).

### 1.5.4 Peer evaluation

There are a number of fMRI investigations of experimentally manipulated social exclusion using the Cyberball task. This task involves participants playing a game of "catch" with two other players under the guise that they are playing with real peers over the Internet. However, the other players are actually preprogrammed to include or exclude the participant. In one study, recruitment of the mPFC during exclusion relative to inclusion was associated with greater self-reported

susceptibility to peer influence in adolescents but not in adults (Sebastian et al., 2011). This study also found age-related differences in right ventrolateral PFC (vlPFC) recruitment during exclusion conditions, with adults recruiting right vlPFC more than adolescents. Another fMRI study using the Cyberball task specifically in a group of adolescents aged 12 to 13 years found recruitment of the right vlPFC during exclusion conditions was negatively correlated with self-reported measures of distress following exclusion (Masten et al., 2009). Together, these studies suggest the vlPFC plays a role in regulating distress following social exclusion and that this region is still developing functionally between adolescence and adulthood. Healthy adolescents who display heightened activity in an area of the brain called the subgenual anterior cingulate cortex while being excluded from peers in Cyberball were more likely to show an increase in depressive symptoms during the following year (Masten, Morelli, & Eisenberger, 2011).

Prompted by research linking good peer relationships to well-being, Masten and colleagues examined how 12- to 13-year-olds respond to witnessing peer rejection in an online game (Masten, Eisenberger, Pfeifer, & Dapretto, 2010). Participants first completed a self-reported measure of trait empathy before participating in an fMRI task where they witnessed peer exclusion in a game of Cyberball. Afterward, they were asked to write a letter to the rejected player as a measure of prosocial behaviour. Activity in the mentalising network was related to observed exclusion compared to observed inclusion. Although recruitment of the dmPFC and ATC appeared to be related to self-reported trait empathy, only the anterior insula showed a positive correlation with prosocial behaviour. Together, these findings suggest that young adolescents recruit the mentalising network more

while witnessing peer rejection than in a situation where peers are being treated equally.

### 1.5.5 Peer influence

Peer influence on conformity shows a curvilinear pattern between middle childhood and late adolescence, reaching a peak in early adolescence (Berndt, 1979). For example, the popularity rankings of a given song influence how much adolescents like it (Berns, Capra, Moore, & Noussair, 2010). In an fMRI task, adolescents aged 12 to 17 years listened to and rated the likeability of short music clips, first without knowing the popularity of the song and then after receiving its popularity ranking. Adolescents' change in song evaluation correlated with increased recruitment of the anterior insula and ACC, which the authors suggest may reflect the anxiety of having preferences that are dissimilar to those of others.

The presence of peers affects how likely adolescents are to take risks in a driving game. Adolescents (13 to 16 years), young adults (18 to 22 years), and adults (24+ years) took around the same number of driving risks when alone, whereas the adolescents took significantly more in the presence of their friends (Gardner & Steinberg, 2005). In contrast, peers had no impact on risk taking in adults and had an intermediate effect on risk taking in young adults (Gardner & Steinberg, 2005). In an fMRI version of this task, in the peers-present condition two friends communicated with the participant (who was in the MRI scanner) over an intercom (Chein, Albert, O'Brien, Uckert, & Steinberg, 2011). Adults aged 24 to 29 years showed higher activity in lateral PFC than did adolescents aged 14 to 18 years or younger adults aged 19 to 22 years when they had to make critical decisions in the driving game, both when alone and when peers were present.

Relative to both groups of adults, adolescents showed increased recruitment of the ventral striatum and orbitofrontal cortex during the driving decisions with peers compared to when alone.

Social context modulates risk attitudes adopted by adolescents (Engelmann, Moore, Monica Capra, & Berns, 2012). Relative to adults, adolescents showed greater risk-adverse behaviour after receiving expert advice, and this effect is modulated by increased engagement of the dorsolateral PFC by adolescents during valuation in the presence of advice (Engelmann et al., 2012). The authors suggest enhanced inhibitory and cognitive control processes may underlie the effect of social context on risky decision making in adolescents.

## 1.6 Animal studies of social sensitivity

Rodent studies indicate that social stress induced by isolation can have long-lasting impacts. Exposure to social isolation during adolescence increases the likelihood of depressive-like behaviours as well as alterations in the structure of the prefrontal cortex (Leussis & Andersen, 2008). A recent study found that rats socially isolated during early adolescence were faster at remembering drug-associated contextual stimuli than rats that were not socially isolated during early adolescence or rats that were socially isolated during late adolescence (Whitaker, Degoulet, & Morikawa, 2013). The socially isolated rats showed enhanced synaptic plasticity in an area of the brain involved in reward-based learning and addictive behaviours, and their drug-associated memories were harder to extinguish (Whitaker et al., 2013). Importantly, later resocialisation of the rats isolated during early adolescence did not reverse the neural changes. This study suggests that early adolescence is a sensitive period for social signals and that

social isolation during this time can change neural mechanisms involved in acquiring and maintaining drug-associated cues, possibly increasing vulnerability to addictive behaviours (Whitaker et al., 2013). Although the study involved rodents, the impact of social isolation on adolescent health and life trajectories likely applies to humans. If so, the consequences of social exclusion can be so great that mechanisms and behaviours promoting peer acceptance are considered adaptive.

The long-lasting effects of stress in adolescence include disrupted social and reproductive behaviour. For example, male rats exposed to chronic social instability stress during adolescence were, in adulthood, more anxious and less socially interactive (Green, Barnes, & McCormick, 2012), showed deficits across many sexual behaviours (McCormick et al., 2013), and had lower plasma testosterone concentrations than rats not exposed to social stressors during adolescence (McCormick et al., 2013). There is also evidence from studies on hamsters that adolescence is a period of increased sensitivity to the organisational effects of testosterone, which in turn affects adult reproductive behaviour (Schulz, Zehr, Salas-Ramirez, & Sisk, 2009). These and many other animal studies (reviewed in Toledo-Rodriguez & Sandi 2011) show that stress exposure during adolescence has a significant impact on the adult. Mild stress exposure during the pubertal transition in rats (postnatal days 28–42) increases risk-taking and novelty-seeking behaviour and decreases anxious behaviour in later adolescence (postnatal days 45–51), suggesting that stress experienced during puberty motivates the rats to hasten independence-building behaviours (Toledo-Rodriguez & Sandi, 2011).

Although much evidence for adolescence as a sensitive period for social processing comes from rodent studies, there is evidence that socio-environmental conditions experienced during human adolescence can impact attitudes toward health and reproduction in young adulthood (Brumbach, Figueredo, & Ellis, 2009). Adolescents within socially unpredictable environments not only experienced decreased physical and mental health in the short term but also adopted faster life history strategies in young adulthood, such as decreased health, less sexual restrictedness, and less resource-accruing potential (Brumbach et al., 2009). Further human studies are needed to investigate whether the adolescent brain is particularly sensitive to cues from the social environment.

## 1.7 Structural brain development

The human brain undergoes profound changes in anatomy across the first decades of life. Neuroimaging methods, such as MRI, have enabled the investigation of these anatomical changes in large, longitudinal samples. In the second part of this introduction, I review the history human brain development studies, and synthesise the results from several longitudinal MRI studies of brain development to update our current knowledge of how the brain develops across adolescence.

### 1.7.1 Histological discoveries and post-mortem work

Research in the 1960s and 1970s provided the first anatomical evidence that the human brain continues to develop beyond childhood (Dekaban & Sadowsky, 1978; Huttenlocher, 1979; Yakovlev & Lecours, 1967). By quantifying the synaptic profiles of layer III in the middle frontal gyrus, Huttenlocher showed that synaptic density in this area is much greater in childhood than in adulthood. At age 7 years, synaptic density in this portion of the prefrontal cortex was 36%

greater than the adult mean, and remained relatively stable between ages 16 and 72 years (Huttenlocher, 1979). Separate post-mortem work looking at myelination cycles throughout the brain provided support that association cortices continue to gain myelin into the second and third decades (Benes, 1989; Yakovlev & Lecours, 1967). These results prompted Yakovlev and Lecours to theorise that these protracted changes in white matter development paralleled behavioural changes occurring at this time, with special emphasis on social navigation.

> "[T]he exponential myelination of the supralimbic division of the hemisphere and cerebral cortex correlates with the exponential maturation of the behavioural patterns in the sphere of motility of effective *societal* transactions – symbolised thought, language and manufacture, and of learning from individual experience." -Yakovlev & Lecours, 1967, p. 63.

Although constrained by small sample sizes that almost entirely exclude the teenage years, these studies challenged the prevailing idea that brain development was complete by early childhood and spurred subsequent work investigating structural brain changes beyond the first decade of life.

Autopsy reports from hospitals in and around the Washington, DC area dating between 1964 and 1973 were pooled together to extract brain weight and other physical data from 4,736 individuals representing ages across the entire life span (Dekaban & Sadowsky, 1978). Brain weight was measured separately for females and males and compared against age, body height, and body weight, demonstrating the relatively dramatic changes in brain weight that occur within the first three years of life as well as the relatively protracted climb to maximum brain weight obtained in the late teen years. The now ubiquitous average sex difference of ~9% greater brain weight in males than females was observed in this

study, crucially relating these differences to measures of body size (Dekaban & Sadowsky, 1978).

### 1.7.2 Magnetic resonance imaging

Although post-mortem work paved much of the way in our understanding both the microscopic and macroscopic changes occurring in the brain across development, MRI has quickly become the instrument of choice to measure changes in brain structure. Without the need for ionizing radiation, MRI is both safe for children and for imaging the same individual multiple times. Although an MRI machine can seem intimidating to young participants, planning visits to the MRI through videos or mock-scanning visits, and friendly scanner operators help to alleviate the anxieties of participants. The main limiting factors to developmental MRI appear to be minimising the amount of noise introduced to the images by factors such as scanner artefacts and participant motion.

## 1.8 What MRI studies measure

MRI is an imaging technique based on the principles of nuclear magnetic resonance that detects proton signals from water molecules and that allows us to produce high quality images of the internal structure of the living brain. MRI differentiates between tissue types, and protocols designed to create anatomical images of the brain can distinguish between grey matter, white matter, and cerebrospinal fluid (CSF) (Figure 1.6). By providing the contrast needed to distinguish these, MRI allows researchers to measure the sizes of different parts of the brain.

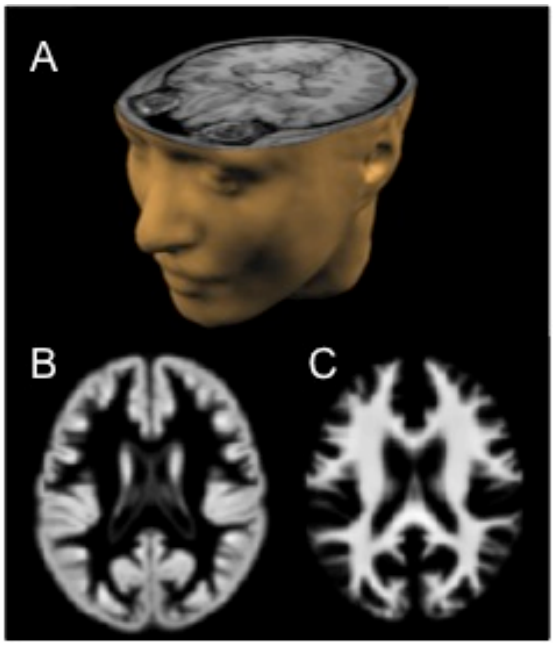


**Figure 1.6. Example of an MRI of a human brain.** MRI differentiates between tissue types, and protocols designed to create anatomical images of the brain can distinguish between grey matter, white matter, and cerebrospinal fluid (CSF). A) The MRI scan of one individual, with one axial slice visible. B) The contrast here highlights the cortical grey matter, and some subcortical grey matter. C) The contrast here is highlights the white matter.

Typical current anatomical images of the brain captured by MRI have a spatial resolution of approximately 1 cubic millimeter ($mm^3$). The volume of an adult human brain is, on average, between 1,131,000 – 1,273,000 $mm^3$, with substantial variation between individuals (Allen, Damasio, & Grabowski, 2002). Although the spatial resolution of modern MRI protocols is very high, $1mm^3$ of cortical grey matter can contain between 10,000 and 60,000 neurons, up to four times as many glial cells per neuron (Ribeiro et al., 2013), as well as neuronal processes, blood vessels, intracortical myelin and dendritic spines. As displayed in Figure 1.7, one study calculated that $1mm^3$ of grey matter in the cortex of a mouse consisted mostly of dendrites and axons (Braitenberg, 2001). However, primate and rodent brains differ on a number of levels, including neuronal size and packing density (Herculano-Houzel, 2009). Currently, we cannot be certain of the microscopic processes that underlie the gross changes in human brain structure captured by

MRI, but by integrating evidence from post-mortem and animal work, we can hypothesise as to what could underlie the signal changes (see section 2.5).

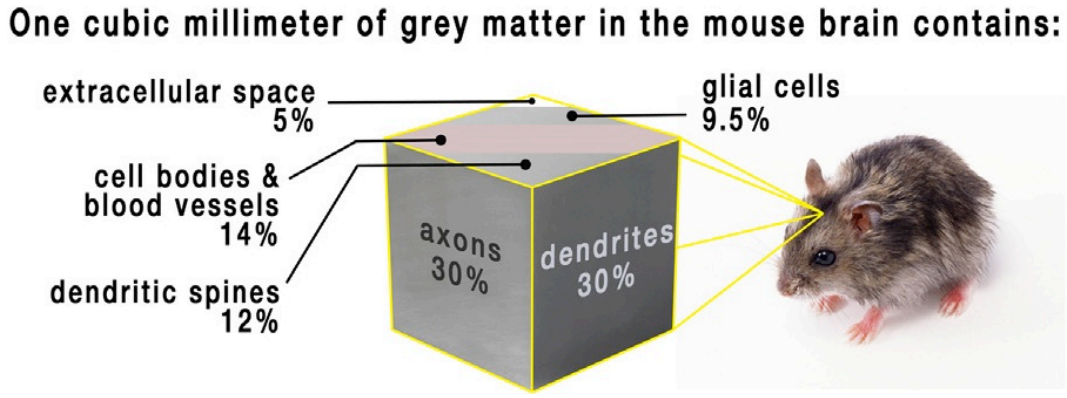


**Figure 1.7. The composition of a cubic millimeter of grey matter in the mouse cortex.** Data derived (and rounded) from Braitenberg (2001).

### 1.8.1 Volume

One of the first introduced and most popular structural measurements of the brain is volume. Before MRI, researchers would measure the intracranial volume of skulls to infer the brain size of individuals (Harper, Kril, Raven, & Jones, 1984). However, given the nature of this method, longitudinal analyses were impossible to conduct. With the advent of brain imaging, we can now measure the volume of an individual's brain as well as the volumes of different tissue types or specific structures, multiple times in the same individual.

### 1.8.2 Whole brain volume

Whole brain volume, sometimes referred to as total brain volume, is typically measured by summing the grey and white matter volumes, excluding the brainstem. However, sometimes whole brain volumes also include non-brain matter such as CSF, ventricles and the choroid plexus. There have been a number of longitudinal imaging studies examining developmental changes in whole brain

volume, several of which were included in a recent meta-analysis (Hedman, van Haren, Schnack, Kahn, & Hulshoff Pol, 2012). Results from this meta-analysis showed whole brain volume increases throughout childhood and early adolescence, until around the age 13 years. After this age, whole brain volume slightly decreases, remaining roughly stable until the mid-thirties. However, changes occurring between mid-adolescence and mid-adulthood might be biased due to the age ranges of the studies included. Furthermore, recent studies that were not included in the meta-analysis provide somewhat mixed results. A study of 103 individuals scanned at least twice across ages 5–32 years did not find any significant overall whole brain volume changes, although a proportion of participants showed volume increases between ages 5–11 years (~50%) and 8–14 years (~35%), and a smaller proportion of participants showed volume decreases between ages 11–19 years (~30%) and 15–22 years (~30%) (Lebel & Beaulieu, 2011). A recent study of 292 individuals (892 scans) scanned between two and four times across ages 4.5–22 years revealed an increase in whole brain volume until mid to late adolescence (Aubert-Broche et al., 2013). These studies call into question the assumption that whole brain volume development is complete in late childhood.

### 1.8.3 Grey matter & white matter volumes

Grey matter is composed of neuronal bodies, glial cells, dendrites, blood vessels, extracellular space and both unmyelinated and myelinated axons. The grey matter that forms the outer ~4mm of the cerebrum is called the cerebral cortex, although grey matter is also found subcortically and in the cerebellum. White matter is composed of myelinated axons, glial cells, and extracellular space. These are the

two major components measured by structural MRI, and each has a distinctive developmental trajectory.

Cortical grey matter volume is greatest in childhood, generally decreases throughout adolescence, and begins to decelerate in volume loss around the early to mid-twenties (Aubert-Broche et al., 2013; Tamnes, Walhovd, Dale, et al., 2013). Studies using the National Institute of Mental Health (NIMH) Child Psychiatry Branch dataset have reported inverted-U shaped patterns of cortical grey matter volume development, with "peak" grey matter volumes attained in late childhood or early adolescence (Giedd et al., 1999; Lenroot et al., 2007; Raznahan et al., 2011), but this has not been replicated in other samples (Aubert-Broche et al., 2013; Lebel & Beaulieu, 2011; Tamnes, Walhovd, Dale, et al., 2013; Wierenga, Langen, Oranje, & Durston, 2014), as detailed below.

The previously mentioned study of 103 individuals scanned at least twice across ages 5–32 years reported a linear decrease in grey matter volume across this age span (Lebel & Beaulieu, 2011). Of the participants scanned between ages 5 and 11 years, over 50% showed a decrease in grey matter volume. This proportion increased to over 80% for 8–14 year olds, 90% for 11–19 year olds, and 80% for 15–22 year olds. The majority of participants scanned between 22 and 32 years showed no change in grey matter volume. In the previously mentioned study of 292 individuals scanned between two and four times across ages 4.5–22 years, grey matter volume showed relative stability between ages 5 and 10 years, and decreased between ages 10 and 20 years, with similar trajectories for both female and male participants (Aubert-Broche et al., 2013). Cortical grey matter volume decreased across ages 8–22 years in a sample of 85 participants scanned twice,

with the steepest decrease roughly coinciding with the teen years (Tamnes, Walhovd, Dale, et al., 2013). Taken together, this study reported a 1.15% mean annual decrease in cortical grey matter volume between late childhood and the early twenties. A similar pattern was found in study of 135 individuals (201 scans) aged 7–23 years (Wierenga, Langen, Oranje, et al., 2014). These four separate longitudinal studies suggest that grey matter volume does not "peak" at a specific age in late childhood or adolescence. Instead, it appears that grey matter is at its highest volume during mid-to-late childhood, and decreases across the second decade (illustrated in Figure 1.8a).

Longitudinal studies consistently report an increase in white matter volume across childhood and adolescence (Figure 1.8b). The Lebel & Beaulieu (2011) study reported an increase in white matter volume between ages 5 and 25 years, with white matter volume stabilising around this time. Over 90% of participants scanned between 5–11 years, 8–14 years and 11–19 years showed an increase in white matter volume. Only half of the sample scanned between 22 and 32 years showed an increase in white matter volume, with the other half showing no change. The Aubert-Broche et al. (2013) study reported an increase in white matter volume across ages 5–20 years, with males showing an almost linear increase and females starting to stabilise in white matter volume in the late teens.

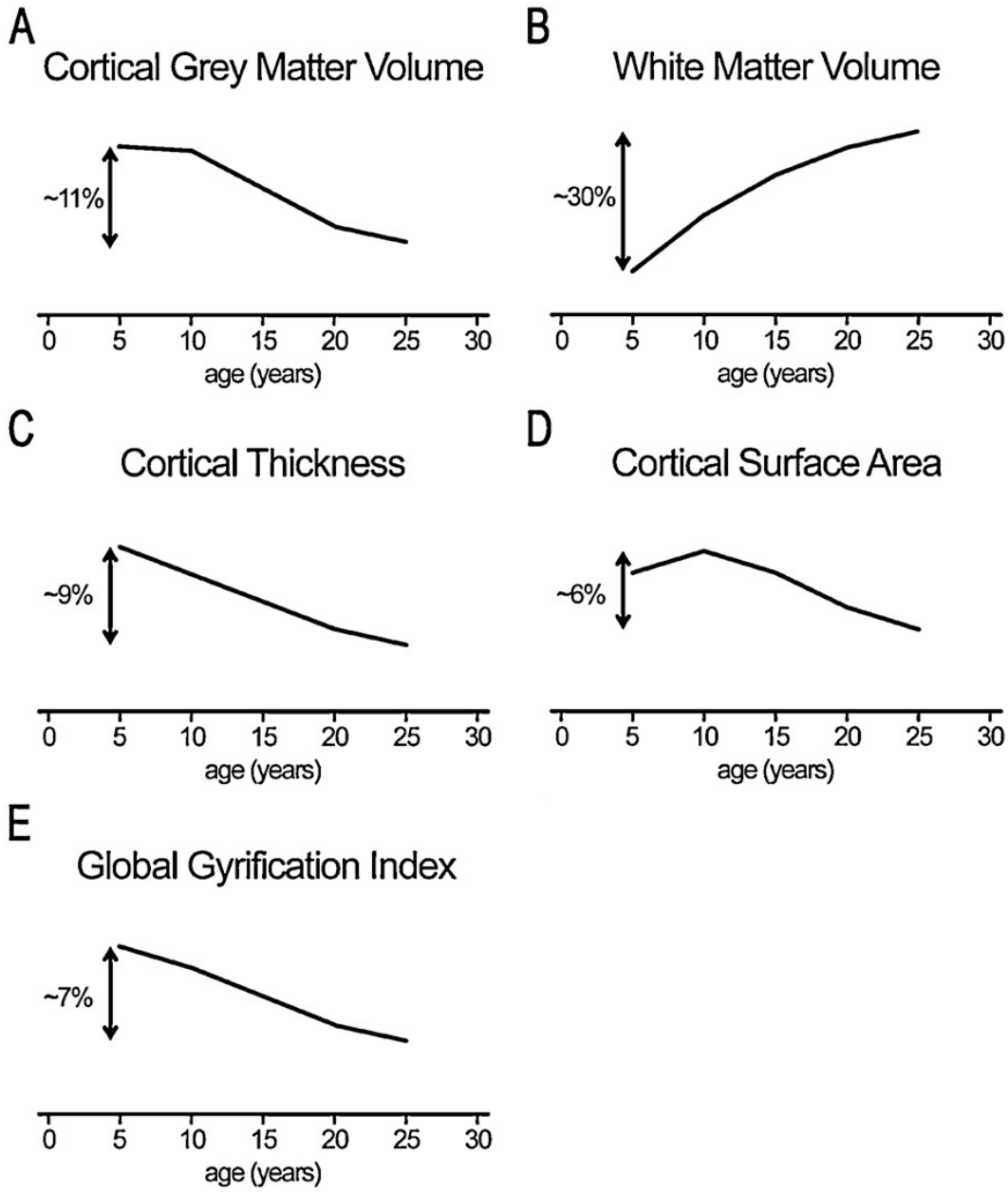


**Figure 1.8. Schematic illustrations of developmental structural MRI findings.** Each schematic drawing is an estimate of the typical developmental trajectory of the measurement of interest, based on current longitudinal studies. The trajectories are broken into five-year increments, and percent changes are estimates based on available data. The measurements include: (A) cortical grey matter volume; (B) white matter volume; (C) cortical thickness; (D) cortical surface area; and (E) global gyrification index. It is important to note that these schematic drawings represent global brain measures, and that specific brain regions could show different developmental trajectories.

### 1.8.4 Regional volumes

While it is possible to describe the overall developmental pattern of cortical grey matter and white matter volumes, there exists substantial heterogeneity in developmental timing between different cortical and subcortical brain regions.

Many studies examine the developmental trajectories of specific lobar volumes, often divided into the frontal, temporal, parietal, and occipital lobes. Some studies have examined cortical regions defined by more fine-grained parcellation methods or a priori regions of interest. Depending on the software and parcellation scheme used, it is possible to measure grey matter and white matter for regional volumes (e.g., FreeSurfer). The Aubert-Broche et al. (2013) study reported similar developmental trajectories for frontal and temporal grey matter volume, which largely resembled the overall pattern for total grey matter volume. However, parietal and occipital grey matter volumes showed an almost linear decline across ages 5–20 years, with the parietal cortex showing a greater decrease than the occipital cortex, in contrast with earlier reports (Giedd et al., 1999; Lenroot et al., 2007). Two separate longitudinal samples have shown that the developmental trajectories for frontal, temporal, parietal, and occipital white matter volumes do not appear to differ much from the whole brain white matter volume trajectory, although they show some variability in the magnitude of change occurring across childhood and adolescence (Aubert-Broche et al., 2013; Lenroot et al., 2007).

### 1.8.5 Subcortical volumes

Subcortical brain structures were some of the first brain structures examined in developmental MRI studies, and their measurement and development continue to be of great interest to developmental neuroscience. Commonly measured subcortical structures include the hippocampus, amygdala, thalamus, globus pallidus, putamen, nucleus accumbens, and caudate. Several longitudinal studies have now investigated the developmental trajectories of these structures, revealing substantial heterogeneity in subcortical brain development. An analysis of 60 individuals, scanned twice across ages 11–18 years, found significant hemisphere

and gender effects for several subcortical structures, as well as interindividual variability (Dennison et al., 2013). For example, the right nucleus accumbens decreased in volume for ~50% of participants, while the left nucleus accumbens increased in volume for ~55% of participants. Overall, the study found increased volume in the hippocampus, pallidum, and left accumbens, decreased volume in the putamen, caudate, thalamus and right accumbens, and no change in amygdala volume across adolescence (Dennison et al., 2013).

These results were overall similar to those found in a sample of 85 individuals scanned twice across ages 8–22 years (Tamnes, Walhovd, Dale, et al., 2013). Across this age range, the caudate, putamen, and nucleus accumbens decreased in volume, whereas the amygdala and hippocampus showed little or no change. The pallidum and thalamus showed a slight decrease in volume, with the largest changes occurring between mid- and late adolescence. In a sample of 275 individuals (711 scans) spanning ages 7–20 years, many subcortical structures showed both age-related and puberty-related changes in volume (Goddings et al., 2013). Across this period of adolescence, the hippocampus and amygdala increased in volume, whereas the nucleus accumbens, caudate, globus pallidus, and putamen decreased. Overall, it thus seems that the medial temporal lobe structures follow different developmental trajectories than most of the other subcortical structures.

## 1.9 Surface-based measures

By identifying the borders between tissue types, surface-based cortical reconstruction software allows for the ability to measure not only grey matter volume, but also cortical thickness, surface area, and gyrification and folding

patterns. I briefly outline these measures and their developmental trajectories below.

### 1.9.1 Cortical thickness

Cortical thickness is typically calculated by measuring the distance between the border between white matter and cortical grey matter, and the border between grey matter and the pia mater. The thickness of the cerebral cortex varies roughly between 2mm and 4mm, with the thinnest cortical regions found in the frontal and occipital poles and the thickest regions found in temporal and insular cortices (Ribeiro et al., 2013).

Different samples have revealed different developmental trajectories for cortical thickness (Figure 1.8c). The first longitudinal study of developmental changes in cortical thickness (n=45, scanned twice) showed widespread cortical thinning between mid to late childhood – with the exception of classical language areas, which showed cortical thickening during this short developmental window (Sowell et al., 2004). The NIMH Child Psychiatry Branch sample of 647 participants (1274 scans) showed that whole brain cortical thickness followed a cubic trajectory, decreasing ~9% between late childhood and the early twenties (Raznahan et al., 2011). Linear global cortical thinning was reported between ages 7 and 23 years in recent study of 135 individuals (201 scans) (Wierenga, Langen, Oranje, et al., 2014). A vertex-based analysis of 137 participants (209 scans), found the majority of the cortex thinning linearly between ages 6 and 29 years, with regions in the lateral prefrontal cortex, medial prefrontal cortex, medial posterior parietal cortex, and temporal-parietal-occipital junction following a quadratic trajectory (Mutlu et al., 2013). Direct comparisons and testing of the

effects of different cortical thickness estimation procedures are likely needed to resolve this inconsistency across studies.

### 1.9.2 Surface area

Cortical surface area can be defined using surface-based measurements in a number of ways. Most commonly, it is calculated as the area of the boundary between the white matter and grey matter – often termed the white matter surface. However, cortical surface area has also been defined as the area of the boundary between grey matter and pia mater (called the pial surface), or it has been calculated as the average of the white matter surface and pial surface. The multiple ways in which cortical surface area can be defined limits how easily one may reproduce or compare values across studies. It is also unclear if these different measures of cortical surface reflect the same underlying processes. Therefore, it is crucial to specify how cortical surface area is calculated to promote greater transparency and potential for replication. The average cortical surface area (white matter surface) of an adult human brain is 154,700 ± 14,600 $mm^2$ (Winkler et al., 2010).

In the NIMH Child Psychiatry Branch sample mentioned above, total cortical surface area followed a cubic trajectory, decreasing ~7% between late childhood and the early twenties (Raznahan et al., 2011). A similar pattern was found in smaller study of 135 individuals (201 scans) aged 7–23 years (Wierenga, Langen, Oranje, et al., 2014) (Figure 1.8d). However, certain areas of the cortex expand more than others during development (Fjell et al., 2013; Hill et al., 2010). In a cross-sectional sample of 331 individuals aged 4–20 years, several regions of the cortex showed more expansion than the mean expansion of the total cortical

surface, including the lateral and medial temporal cortex, cingulate cortex, retrosplenial cortex, lateral orbitofrontal cortex, superior frontal gyrus, inferior frontal gyrus, insula, temporoparietal junction, cuneus, and lingual gyrus (Fjell et al., 2013).

### 1.9.3 Gyrification & folding patterns

The human cortex is highly convoluted, with approximately one third of the cortical surface exposed on gyri, and two-thirds buried within sulci. The complexity of cerebral folding patterns has been of great interest to brain imaging research, and recent methods have made the quantification of these folding patterns easier. The gyrification index of the whole brain is defined as the ratio of the total folded cortical surface over the total perimeter of the brain (Zilles, Armstrong, Schleicher, & Kretschmann, 1988), whereas the local gyrification index measures the degree of cortical folding at specific points of the cortical surface (Schaer et al., 2008). The gyrification index of the human brain decreases between childhood and young adulthood, whereas the amount of exposed cortical surface increases from childhood to mid-adolescence (Raznahan et al., 2011), and between middle and late adolescence (Alemán-Gómez et al., 2013). A study of 52 adolescents scanned twice between ages 11 and 17 years showed an overall flattening of the cortex during adolescence, related to decreases in sulcal depth and increases in sulcal width (Alemán-Gómez et al., 2013). Similar to other structural measurements, the development changes in local gyrification varies across the cortex, with regions in medial prefrontal cortex, occipital cortex, and temporal cortex undergoing little to no change between ages 6 and 29 years (Mutlu et al., 2013). However, similar to what has been found in whole brain (Raznahan et al., 2011) and lobar-level (Alemán-Gómez et al., 2013) analyses,

Mutlu et al. (2013) observed linear decreases in local gyrification index across the majority of the cortex (Figure 1.7e).

## 1.10 Brain development before age 5 years

The studies covered in this chapter focused on what we know about structural brain development across adolescence from longitudinal studies. However, it is important to note that the human brain undergoes perhaps its most dramatic development between the prenatal period and early childhood. Recent longitudinal studies show that while major structural landmarks (sulcal pits) are already in place and relatively stable by birth (Meng, Li, Lin, Gilmore, & Shen, 2014), the human brain increases in grey matter volume, cortical thickness and surface area between birth and 2 years (Gilmore et al., 2012; Li et al., 2013). Specifically, cortical surface area more than doubles itself in this time and cortical thickness increases to almost adult levels (~36% between birth and 2 years) (Lyall et al., 2014). This cortical expansion is accompanied by a ~22% increase in in global gyrification between birth and age 2 years (Li et al., 2014).

## 1.11 Conclusion

Adolescence is a period of biological and social transition. Neuroimaging and behavioural studies in humans, and neuroanatomical and behavioural studies in animals, have demonstrated that the social brain and social cognition undergo a profound period of development in adolescence. As such, adolescence might represent a sensitive period for the processing and acquisition of social knowledge.

# Chapter 2 Methods and considerations for longitudinal structural brain imaging analysis across development

## 2.1 Introduction

The human brain undergoes profound changes in structure across development. Several longitudinal magnetic resonance imaging (MRI) investigations of brain development in childhood and/or adolescence are currently underway, with more beginning each year (see Table 2.1). The questions addressed by these investigations are diverse, with some exploring genetic and experience-dependent changes, and others relating changes in brain structure to well-being, behaviour, or cognitive development. Despite the diversity of topics for investigation, each of these studies uses methods to process and analyse brain images acquired longitudinally. This chapter discusses the variety of methods to process, analyse and model longitudinal changes in brain structure, the biological validity of interpretations derived from these investigations, as well as the benefits of longitudinal designs, and best practices in longitudinal studies of brain development.

**Table 2.1**. A non-exhaustive list of longitudinal MRI projects examining developmental changes in brain structure in childhood and/or adolescence.

| Dataset | Participants (age range) | Location | Years | Website |
|---|---|---|---|---|
| NIMH Child Psychiatry Branch | ~2000 participants (5–60 years) | NIMH; Bethesda, MD | 1991–2011 | http://www.intramural.nimh.nih.gov/chp/index.html |
| Leonard Florida sample | 45 participants (5–12 years) | Alachua County, FL, USA | 1999–2004 | http://www.kidsbrains.org/index.php |
| NIH MRI Study of Normal Brain Development | 433 participants (4–18 years) | Six Locations; USA | 2001–2007 | http://www.pediatricmri.nih.gov/ |
| Department of Psychology, University of Minnesota | 191 participants (9–24 years) | Twin Cities, MN, USA | 2004– | http://www.psych.umn.edu |
| The Netherlands Twin Register BRAINSCALE | 190 participants (9–12 years) | Utrecht, The Netherlands | 2005– | http://www.tweelingenregister.org/onderzoek/lopend-onderzoek/brainscale/ |
| NICHE | 147 participants (7–23 years) | Utrecht, The Netherlands | 2006–2011 | http://www.niche-lab.nl/ |
| Neurocognitive Development | ~200 participants (8–25 years) | Oslo, Norway | 2008– | http://www.oslobrains.no |
| PLING | 105 participants (5–8 years) | San Diego, CA, USA | 2010– | http://www.chd.ucsd.edu/research/pling-study.html |
| Laboratory of Neurocognitive Development | 129 participants (8–28 years) | Pittsburgh, PA, USA | 2010– | https://www.lncd.pitt.edu/wp/ |
| Mother-Child Cohort Study | ~350 participants (4–10 years) | Oslo & Trondheim, Norway | 2011– | http://www.oslobrains.no |
| BRAINTIME | 299 participants (8–25 years) | Leiden, The Netherlands | 2011– | http://www.juniorhersenen.nl/braintime |
| U-Change | 300 participants (14–24 years) | Cambridge & London, UK | 2012– | http://www.nspn.org.uk/ |
| Tokyo Teen Cohort Project | 300–400 pairs (9–12 years) | Tokyo, Japan | 2012– | http://www.ttcp.umin.jp/about/ |

## 2.2 Methods of processing structural brain images

Like with functional MRI, there are several ways to process structural brain images. First, in structural MRI studies it is relatively common to acquire multiple T1 weighted sequences from each individual at each time point. One of the first choices during processing is thus whether to combine these in order to increase the signal-to-noise ratio, or to only include the highest quality sequence from each scan sessions (see discussion about quality control below in section 2.2.3). Although averaging sequences will usually increase the signal-to-noise ratio, the effects of data averaging on various structural measures are not well investigated (X. Han et al., 2006; Jovicich et al., 2009) and this might not be the best approach if the number of available high quality sequences varies across individuals or time points. A general recommendation is thus to stick to one of these approaches consistently within a study, and avoid mixing averaged and single acquisitions if possible. Second, while many early studies on structural brain development used hand-tracing methods, there now exists several automated programs that researchers can use to segment the entire brain in a fraction of the time needed to hand-trace individual brain structures. However, some automated software is available for public use, whereas other programs are limited to collaborators, and quality control is always a concern for automated methods. I briefly detail several methods that are in current use for processing structural MRI, as well as essential quality control procedures, below.

### 2.2.1 Manual tracing

Early MRI studies relied on trained individuals to hand trace major brain divisions and structures. This technique is still used today, but remains less practical as datasets grow larger. However, some investigators still prefer to use manual

tracing methods for structures that are particularly difficult to segment using automated procedures, such as the amygdala (Morey et al., 2009). The cost for this preference is high, as it is estimated that the amygdala takes around two hours for a trained expert to trace by hand (Hanson et al., 2012), and reliability and reproducibility is always a concern when relying on manual tracing. To overcome the persistent challenges of segmenting the amygdala, Hanson and colleagues (2012) developed a method that requires a small proportion of hand-traced scans (~20) to train an automated machine learning-based segmentation procedure to accurately segment the amygdala in large samples.

### 2.2.2 Automated software

Many automated programs have emerged over the past 20 years (selected automated software displayed in Table 2.2). The reliability of automated methods is likely to vary amongst programs and across brain structures, but there have been a few studies comparing estimates obtained by automated methods with those obtained through manual tracing. For example, FreeSurfer's estimates for cortical thickness have been validated against both histological analysis (Rosas et al., 2002), and manual tracing (Kuperberg et al., 2003; Salat et al., 2004). Automated subcortical segmentation of the amygdala and hippocampus has also been compared against manual tracing efforts (Morey et al., 2009). Scan-rescan reliability varies among subcortical structures segmented with automated methods, with some subcortical structures showing higher reliability (e.g., thalamus) than others (Morey et al., 2010). An analysis of 31 children (4–11 years) found that automated software using surface-based registration was more accurate than volume-based registration methods, and that registering these still-developing brains to a common space did not introduce age-related biases (Ghosh

et al., 2010). The variety of programs and techniques available to define brain measurements introduces challenges to replication efforts. While there have been studies comparing brain measurements estimated by voxel-based and surface-based programs (Winkler et al., 2010), there have been relatively few studies comparing measurements between specific automated programs.

| Software | Description | Methods Papers | Measurements | Notes |
|---|---|---|---|---|
| **3D Slicer** | Software package for visualization and image analysis. | Fedorov et al., 2012 | Cortical volume, Subcortical volume, DTI | Freely available; Open Source; Ongoing updates |
| **AFNI** | Software package for mapping human brain activity, with add-on programs and toolboxes that allow for cortical surface-based analysis (SUMA), and DTI tractography analysis (FATCAT). | Cox, 1996; Cox & Hyde, 1998; Taylor & Zaad, 2013 | Cortical volume, Subcortical volume, DTI | Freely available; Open Source; Ongoing updates; Interacts with FreeSurfer and FSL |
| **Caret** | Surface and volume-based software package for structural and functional analyses of the cerebral and cerebellar cortex. | Van Essen & Dierker, 2007; Van Essen, 2011 | Surface measures, Myelin mapping, Cortical depth | Freely available; Open Source; Ongoing updates; Interacts with FreeSurfer |
| **CIVET** | Surface-based human brain image-processing pipeline for corticometric, morphometric and volumetric analyses. | Zijdenbos et al., 2002 | Cortical thickness, Surfrace area, Mean curvature, Gyrification index | Freely available; Ongoing updates |
| **FreeSurfer** | Surface- and volume-based software suite for processing and analyzing brain MR images. FreeSurfer reconstructs the cortical surface, segments subcortical structures, and provides a number of labelling and statistical analysis options. | Dale et al. 1999; Dale et al. 2002; Fischl et al. 1999; Reuter et al., 2012 | Cortical volume, Subcortical volume, Cortical thickness, DTI, Surface area, Mean curvature, Gyrification index | Freely available; Open Source; Ongoing updates; Interacts with Caret and FSL; Calculates DTI metrics via TRACULA; Has longitudinal pipeline |
| **FSL** | Comprehensive library of analysis tools for fMRI, MRI and DTI brain imaging data. | Jenkinson et al., 2012; Smith et al., 2004 | Gray matter concentration, volumetry, DTI, fMRI | Freely available; Ongoing updates; Interacts with FreeSurfer |
| **LL method** | The Longitudinal registration and Longitudinal classification (LL) method measures structural volume changes in longitudinal MRI scans in which participant-specific information is used for both registration and segmentation. | Aubert-Broche et al., 2013 | Cortical volume, Subcortical volume | Not available for public use; Specific to longitudinal designs |
| **QUARC** | Quantitative anatomical regional change (QUARC) is a nonlinear registration method that measures longitudinal change on a voxel-wise basis. | Holland et al., 2011 | Cortical volume, Subcortical volume | Not available for public use; Specific to longitudinal designs; Interacts with FreeSurfer |
| **VBM** | Voxel-based morphometry (VBM) is a technique that measures the concentration of grey matter within each voxel of the brain, and provides voxel-wise comparisons of local tissue volumes within a group or across groups. | Ashburner and Friston, 2000 | Grey matter concentration or signal intensity | Freely available; Ongoing updates; Has longitudinal pipeline; Interacts with SPM |

**Table 2.2**. A non-exhaustive list of automated software used to process structural MRI data.

Reliability across scanner manufacturers and field strengths has been assessed as high for FreeSurfer (X. Han et al., 2006; Jovicich et al., 2009; Reuter, Schmansky, Rosas, & Fischl, 2012). Nonetheless, a general recommendation that holds across software methods is to, if possible, avoid mixing scans from different scanners, field strengths, protocols and scanner software versions in the same study, and furthermore to avoid mixing different processing software versions during analyses. This is especially important in longitudinal studies and if these potentially confounding variables are related to age, time point, sex or other study parameters. However, large-scale multi-site studies are a possible exception, given that they provide larger samples than usually possible in single-site studies and, therefore, the possibility to investigate the consistency of effects, and the ability to statistically control for site, hardware or software related variables. But even in such large-scale studies, effort should be devoted to evaluating and adjusting the scanners and sequences used, as for instance done in the Alzheimer's Disease Neuroimaging Initiative (Jack et al., 2008), and extensive analyses of the effects of potentially confounding factors are recommended.

### 2.2.3 Quality control

Like all data, structural MRI data requires quality control procedures to reduce noise and guard against spurious findings. One aspect of quality control can occur right after scans are acquired, through visual inspection of the raw images. Visual inspection for gross abnormalities by a trained individual or radiologist is standard for many protocols, and most studies of typical development will remove individuals with any neurological issues. However, visual inspection should also be conducted to identify and document any artefacts due to head motion or

scanner peculiarities. Systematic artefacts can bias data and affect results, even in large datasets.

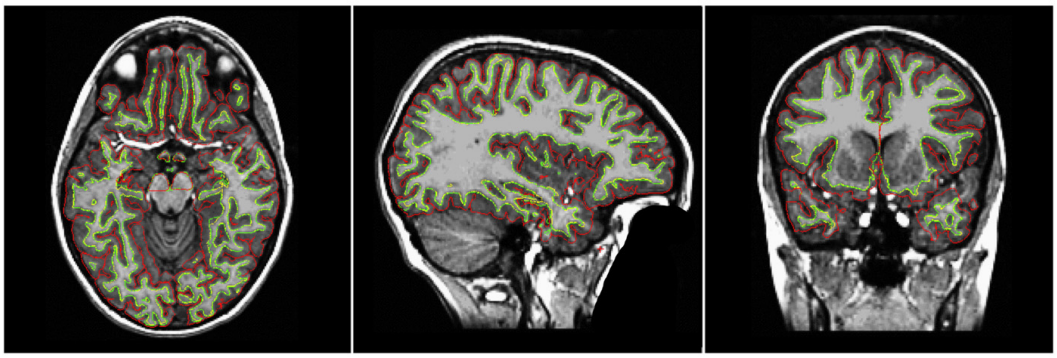

**Figure 2.1. One quality control consideration for structural MRI**. This figure illustrates one participant's surface-based cortical reconstruction (using FreeSurfer 5.3). The yellow-green line indicates the boundary between the white matter and grey matter and the red line indicates the boundary between grey matter and pia mater. This T1 image passed visual inspection with no visible motion artefact, and the majority of the cortex was adequately reconstructed. However, the automated program failed to reconstruct the anterior temporal cortex.

Visual inspection procedures should also be implemented after scans have been processed to ensure that there were no errors in the segmentation or reconstruction processes (see Figure 2.1). Automated methods are susceptible to biases introduced by motion artefact, which could make grey matter volumes appear smaller (Blumenthal, Zijdenbos, Molloy, & Giedd, 2002). Detailed quality control processes can be found in the documentation of many software programs listed in Table 2.2. Solely controlling for the quality of T1 images does not guarantee a sample of flawless post-processed brain segmentations or reconstructions. Two recent conference presentations addressed potential biases in developmental trajectories due to excessive head motion in younger participants (Alexander-Bloch et al., 2012; Stockman, Alexander-Bloch, Raznahan, & Giedd, 2012), but this concern has yet to be addressed in detail in published reports. Many studies provide descriptive accounts of their quality control procedures (Dennison et al., 2013; Nguyen et al., 2013), which are becoming increasingly important given the

variety of methodologies used in longitudinal brain development studies. Moreover, the field would also benefit from an increased focus on quantitative head motion detection and measurement, as well increased use of both prospective and retrospective motion compensation procedures, and the inclusion of such measurement and procedures in commonly used software packages (Yendiki, Koldewyn, Kakunoori, Kanwisher, & Fischl, 2014). Motion-related artefacts in developmental studies of structural MRI likely requires a similar level of awareness and consideration as has been shown for functional MRI in the past few years (Fair et al., 2012; Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Yendiki et al., 2014).

## 2.3 Modelling brain development

In longitudinal designs with multiple time points, simple regression analyses cannot be used because brain measures taken from the same individual across time are not independent of each other. Therefore, statistical methods that take into account the effects of continuous dependent (within-participant) and independent (between-participant) variables are necessary. Complexity is added when we consider the non-linearity of brain development. There are a variety of analysis techniques commonly used for developmental trajectory analysis – some of which go by multiple names, which I discuss briefly below.

*Multilevel modelling* (also known as: mixed models, mixed-effects models, hierarchical linear models): Multilevel models estimate the fixed effects of a chosen variable (e.g., age, pubertal status) on a measure of interest (e.g., grey matter volume, cortical thickness), while also taking into account the within-participant dependence of observations. This technique has the flexibility to

model data that has been collected at uneven intervals, and does not require all participants to have the same number of data points. The models can have fixed or variable intercepts and slopes, depending on the hypothesis. Multilevel models are often used to generate population-level trajectories, but can also be used to compare the developmental trajectories between groups and to examine individual differences. These individual differences can be modelled by including random effects for the intercept and slope of the time variable. In non-linear models, the independent variable is often centered to reduce correlations between the different terms. There have been many books written on this topic, but Singer & Willett's *Applied Longitudinal Data Analysis* is a particularly relevant guide for multilevel analysis of longitudinal brain imaging data (Singer & Willett, 2003). Various methods exist that perform multilevel modelling, and I have highlighted a few of these in Table 2.3.

*Latent Growth Modelling* (also known as: latent growth curve analysis, growth mixture modelling, latent variable analysis) is another method used to analyse developmental trajectories with longitudinally acquired data, but is distinguishable from multilevel modelling because it involves structural equation modelling (Hox & Stoel, 2005). Structural equation modelling uses latent variables – unobserved variables that are inferred from measured variables – to account for relationships between observed variables. Unlike multilevel models, latent growth models require participants to have been measured at similar time intervals. This makes latent growth modelling problematic for unstructured longitudinal designs, where participants are scanned at different ages or developmental milestones.

| Study | Journal | Method | Software | Measure |
|---|---|---|---|---|
| Giedd et al., 1999 | Prog in Neuro-Psychopharm and Bio Psychiatry. | NLMM | PROC MIXED in SAS | Subcortical volumes |
| Lenroot et al., 2007 | Neuroimage | NLMM | SPSS | Cortical and subcortical volumes |
| Lebel and Beaulieu, 2011 | J Neuroscience | LMM | ExploreDTI and Freesurfer | Whole brain, white and grey matter volumes |
| Raznahan et al., 2011 | J Neuroscience | NLMM | nlme in R | Cortical volume, thickness, surface area and gyrification |
| Mills et al., 2012 | SCAN | NLMM | nlme in R | Cortical volume, thickness and surface area |
| Nguyen et al., 2013 | Cereb Cortex | LMM | SurfStat, SPSS | Cortical thickness |
| Mutlu et al., 2013 | Neuroimage | NLMM | Matlab R2012a | Cortical thickness and gyrification |
| Dennison et al., 2013 | Dev Science | HLM | Stata | Subcortical volumes |
| Aubert-Broche et al., 2013 | Neuroimage | NLMM | nlme in R | Cortical and subcortical volumes |
| Ordaz et al., 2013 | J Neuroscience | HLM | HLM Version 6 | fMRI |
| Goddings et al., 2013 | Neuroimage | NLMM | nlme in R | Subcortical volumes |

HLM: Hierarchical Linear Models; LMM: Linear Mixed Models; NLMM: Nonlinear Mixed Models

**Table 2.3**. Statistical methods used to analyse longitudinal MRI data in a selected group of studies.

### 2.3.1 Physiological plausibility

When choosing growth models for structural brain measures, it is essential to consider the physiological plausibility of the model. This depends on the developmental period, the age span covered, and the brain measure being examined. For example, it might be physiologically plausible for cortical thickness to decrease almost linearly across adolescence, whereas it might not be plausible across the first decade of life or across adulthood and senescence. The cubic age model that has often been fitted to various cortical brain measures (e.g., grey matter volume) is physiologically plausible in an age range that spans childhood, adolescence and young adulthood; given that cortical grey matter volume tends to be greater in childhood than in adulthood. Quadratic models should work for shorter age spans, where it is not expected for one end of the age span to show relative stability. Linear models might be the best fit for age ranges where steady change is likely. However, if one is interested in more precisely mapping and describing developmental trajectories and in interpreting e.g. exact peaks or break-points, nonparametric local smoothing techniques (e.g. the smoothing spline) are likely to be more accurate, since global fits such as quadratic models may be affected by irrelevant factors, as discussed below.

### 2.3.2 Comparing brain developmental trajectories

Previous studies have used a variety of strategies in deciding the best fitting model of a brain measure. Early studies using the NIMH Child Psychiatry Branch sample adopted a step-down model selection procedure to determine if cubic, quadratic and linear age effects best fit the data. Using this technique, the most complex model (i.e., cubic model) is selected if it is a significant fit at $p < 0.05$. Current statistical procedures suggest using the heuristic of parsimony (i.e.,

Occam's Razor) in selecting the best model, which means finding a model that explains the most amount of variance using the least number of parameters. This is often achieved by likelihood ratio tests or comparing the Akaike Information Criteria (AIC) values of different models. AIC can be used to compare models that are not nested because it is a standardised measure of the goodness of fit of a chosen model, while penalising the model for complexity. A lower AIC value reflects a better fit to the data. Final reported values should take into account how much better the selected model is over the null, or baseline, model. For example, a previous study found that cortical thickness in specific areas of the cortex (e.g., temporal pole, occipital pole), did not significantly change between ages 6 and 29 years (Mutlu et al., 2013). Without taking the null model into consideration, a study could potentially report an erroneous developmental effect.

Comparing the developmental trajectories of different brain structures, or the same brain structures between groups, can be difficult. Brain structures that follow different non-linear developmental trajectories are particularly difficult to compare to one another. One strategy is to calculate annualised rate of change or standardised rate of change across brain regions (Goddings et al., 2013; Lenroot et al., 2007; Tamnes, Walhovd, Dale, et al., 2013). Using this strategy, it is possible to compare the amount of change occurring at different age periods for different brain regions.

Many studies are interested in comparing developmental trajectories between groups, such as females and males. However, if the compared groups follow different developmental patterns (e.g., quadratic and cubic) for the measurement of interest then it is not easy to statistically determine the difference. Some studies

reporting inverted-U shaped trajectories have calculated the age at reaching the "peak" of a certain measure by solving the first-order derivative of the growth trajectory equation. While this is an attractive method of calculating a comparable value, determining the inflection point of a growth model is sensitive to potential biases, including the age range of sample, the selected model, and any measurement error (Fjell et al., 2010). In addition, these peak ages have often been reported without confidence intervals, without which small differences might be exaggerated.

### 2.3.3 Correcting brain measures

Some developmental studies comparing brain structure differences longitudinally have corrected or controlled for intracranial volume (Nguyen et al., 2013), whereas others have not performed any type of such correction (Aubert-Broche et al., 2013; Goddings et al., 2013). Rather than correcting or controlling for individual variability in intracranial volume – a composite of not only brain tissue (~80%), but also blood (~10%) and CSF (~10%) (Rengachary & Ellenbogen, 2005), many have opted to correct for whole brain volume. However, such correction in developmental samples might be problematic given that whole brain volume increases until around the age of 13 (Hedman et al., 2012). In addition, given that different components of the brain develop at different rates, controlling for whole brain volume could potentially bias results (Barnes et al., 2010). The impact of correcting or controlling for intracranial or whole brain volume in longitudinal developmental samples has not yet been systematically studied. If corrections are performed, it is therefore useful to also report the uncorrected results and the developmental effects on the measure used for correction.

## 2.4 Relating biological development to brain development

It is essential to relate developmental trajectories to an appropriate scale. Across fields, most developmental studies use chronological age to quantify development. However, there are also other developmental processes that occur during the first two decades of human development which likely impact on brain development, such as body growth and puberty.

### 2.4.1 Age

Age is easily quantified with high reliability and validity and therefore allows easy comparison across studies and investigative techniques. Furthermore, it provides a linear scale throughout the human life cycle, allowing studies to compare absolute and relative growth at different stages of life (Tamnes, Walhovd, Dale, et al., 2013). Multi-model brain imaging pattern analysis techniques show that aspects of brain structure can predict age with high accuracy (Brown et al., 2012). Many of the longitudinal studies described in the introduction have modelled brain development during childhood and adolescence against age, and it remains the most popular measure of biological development.

Whilst many brain imaging studies have related brain development to age, considerable individual variability exists, and age only explains a certain proportion of the variance in modelled trajectories. One limitation of using age as a measure against which to judge brain development is that it provides little information on the underlying physiological mechanisms. During late childhood and adolescence, individuals undergo physical changes such as a height growth spurt and puberty, which happens at different ages across individuals. These other physical measures are discussed in the following sections.

### 2.4.2 Body size

A linear relationship between brain mass and body mass exists for the primate species, with human brains deviating by only ~10% from its expected size (Azevedo et al., 2009; Herculano-Houzel, Collins, Wong, & Kaas, 2007). New evidence has revised the previous theories about the relationship between human brain mass and body mass. It appears that humans do not have a larger brain than would be expected for a primate of our body mass, but instead that other primates, such as orangutans and gorillas, have larger bodies than would be expected (Herculano-Houzel et al., 2007). Further, brain mass and body mass are only correlated, and brain size does not appear to be determined by body mass (Herculano-Houzel, 2009). Specific genes are related to both brain mass and body mass (Silver et al., 2010), however the mechanisms linking the two remain largely unknown. Recent anthropological research suggests that the increase in brain mass in the genus *Homo* around 300,000 – 138,000 years ago occurred independently of increases in body mass (A. Gallagher, 2013). To date, there have been few studies examining brain size against body size within a large group of humans, or using a longitudinal design.

The relationship between body size and brain size continues to influence the debate regarding sex differences in the brain. Although the, on average, larger brain size of human males compared to human females is often attributed to the, on average, larger body size of males, it is not certain if empirical studies support this notion. One controversial analysis of over 1000 post-mortem human brains found that males were still about 100g heavier than female brains after correcting

for body height or body surface area (Ankney, 1992). However, the validity of the statistical methods used in this study have been questioned (Forstmeier, 2011).

### 2.4.3 Puberty

Changes in brain structure during adolescence can also be related to the hormonal changes underlying the onset of and progression through puberty. Pubertal onset varies by as much as 4–5 years across individuals (Parent et al., 2003), which can introduce substantial variation into studies of brain development between childhood and adolescence if only age is measured. A recent review highlighted several genetic mechanisms that interact with the neuroendocrine system to initiate puberty (Ojeda & Lomniczi, 2013).

Previous structural brain imaging studies have attributed developmental trajectory characteristics to pubertal onset (Giedd et al., 1999; Lenroot et al., 2007). Gender differences in reported grey matter volume "peaks" have been attributed to the discrepancy in pubertal timing between females and males. For example, in studies using the NIMH Child Psychiatry Branch dataset, the 1–2 year difference in "peak" cortical grey matter volumes of females compared to males is described as "corresponding to the average age difference at puberty" (p. 1071, Lenroot et al., 2007). Indeed, clinical endocrinology studies suggest that pubertal development in females is, on average, 1–2 years earlier than in males (Bordini & Rosenfield, 2011; Sun et al., 2002). However, although the age of onset for pubertal milestones is different, the age at which females and males attain the final milestones of puberty (menarche and testes development, respectively) overlap substantially (11.0–14.1 years for females, 11.5–16.5 years for males) (Bordini & Rosenfield, 2011). Furthermore, multiple studies have failed to find

gender differences in cortical grey matter volume trajectory shape (Aubert-Broche et al., 2013; Wierenga et al., 2014), suggesting that if a relationship between cortical grey matter volume and puberty does exist, age alone might not be sensitive enough to detect it. Future work combining different measures of physical maturity, such as height, pubertal status and hormones, may help elucidate the different mechanisms underlying brain development during the transition from childhood to adolescence.

## 2.5 Physiological mechanisms underlying structural changes

What does a reduction in grey matter volume, assessed by a T1 weighted MRI, reflect on a cellular level? Do changes in brain structure during development reflect the same processes as changes observed during adulthood? What are the limitations in MRI, and can we extrapolate the microcellular mechanisms underlying these macrostructural changes? Although these questions remain unanswered, they are crucial to developmental neuroscientists, as they link efforts in neuroimaging to neurophysiological and anatomical research.

### 2.5.1 In development

The underlying mechanisms of developmental changes in structural MRI measures are still debated. To date, there are no studies that have directly tested the relationship between developmental changes in morphometric MRI measures to changes in cellular or synaptic anatomy. However, many studies propose that reductions in grey matter volume during adolescence partly reflect synaptic pruning (Blakemore, 2008; Giedd et al., 1999). While synaptic densities in selected regions of the prefrontal cortex are at their greatest levels at some point during the first two decades, and appear to decrease throughout the second and

third decade (Huttenlocher & Dabholkar, 1997; Petanjek et al., 2011), we cannot directly relate these data to findings in MRI. For one, synaptic boutons (also known as synaptopil) are incredibly small, comprising only a fraction of grey matter volume (Bourgeois & Rakic, 1993). Even when synapses are particularly dense, they are estimated to represent only 2% of a cubic millimeter of neuropil or less than 1.5% cortical volume (Bourgeois & Rakic, 1993). Given this relatively small percentage, it is unlikely that the marked decreases in cortical volume observed across adolescence are purely reflective of synaptic pruning. The reduction in number of synapses might, in addition to a reduction in neuropil, also be accompanied by a reduction in the number of cortical glial cells. These events could together account for more of the cortical structural changes observed during development, although this remains purely a speculation. Other processes, such as the encroachment of subcortical white matter, or continued intracortical myelination, also likely impact on measurements of cortical grey matter, by changing the signal intensity values and contrasts such that the boundary between white and grey matter is moved outwards with increasing age. Undoubtedly, there is a myriad of both parallel and interacting neurobiological processes underlying the macrostructural changes observed during childhood and adolescence in MRI studies.

### 2.5.2 Pre- and post-intervention

While the high degree of plasticity in childhood and adolescence allows for a lot of experience dependent structural change, the neuroanatomical and physiological changes that underlie many of the common MRI changes in the developing brain are likely at least partly different from those underlying experience or training-induced changes in the adult brain (Zatorre, Fields, & Johansen-Berg, 2012).

Although changes in MRI measurements should be similarly reflective of changes in the various neuroanatomical components that make up the measure of interest (e.g., grey matter volume), the mechanisms and specific changes could be different. For example, synaptic changes in adulthood are not nearly as large as the changes observed during the first two decades. The neuroanatomical pioneer Peter Huttenlocher stated that “there is no evidence for any large net increase in synapses in the cerebral cortex during the adult years” (p.173, 2002). Huttenlocher supposed that any new synapses formed in adulthood are "likely to be balanced by loss of other synaptic connections." Similarly, the majority of stable dendritic spines are formed during development. One rodent study showed that only a small percentage of dendritic spines formed by learning (or novel experiences) in the adult mouse are retained (Yang, Pan, & Gan, 2009). Still, changes in synapses and dendritic spines continue to be a popular explanation for MRI volume changes observed in adult training studies. Animal studies that combine MRI and histological measures can contribute to our understanding to some extent. One such study in rodents suggests that training induced changes in MRI volumes are more reflective of changes in neural processes rather than an increase in neural cell size or number (Lerch et al., 2011). As reviewed in Zatorre et al. (2012), multiple neuroanatomical processes could underlie training or experience-induced changes in structural MRI volumes, but many of these possibilities have yet to be investigated.

## 2.6 The benefits of longitudinal designs

This chapter focuses on the methods and results from longitudinal analyses of structural MRI data. Most studies reviewed in the introduction chapter employed accelerated longitudinal designs to allow for investigation of wider age ranges.

There have also been a number of cross-sectional studies investigating structural brain development that use large samples (Brain Development Cooperative Group, 2012; Koolschijn & Crone, 2013; Østby et al., 2009). However, longitudinal samples require far fewer participants than cross-sectional studies in order to detect small differences in brain structure (Steen, Hamer, & Lieberman, 2007). For example, a sample size of at least 146 participants is necessary to have adequate power to detect a 5% difference in whole brain volume between groups in a cross-sectional design, whereas only 4 participants are required to detect changes of similar magnitude in a longitudinal design (Steen et al., 2007). Cross-sectional studies require many more participants because comparative differences are affected by both measurement precision and natural variation in brain sizes – a proportion of which will not likely be relevant. However, measurement precision is the only factor that can affect the required sample size necessary to detect subtle differences in longitudinal studies. Furthermore, there are also a number of other challenges involved in drawing inferences about developmental processes from cross-sectional studies (Kraemer, Yesavage, Taylor, & Kupfer, 2000).

### 2.6.1 Interindividual variability

Individuals vary substantially in brain size. Studies of adults have reported wide variability in whole brain volume, ranging from 974.9 to 1498.5 $cm^3$ (Allen et al., 2002), and 783 to 1414 mL (Steen et al., 2007). These figures suggest that whole brain volume can vary by up to 81% across adults. As would be expected, this variability in whole brain volume is also observable for specific tissue types and other measures of brain morphometry. A study of 486 individuals aged 26–85 years showed wide variability between participants for grey matter volume and surface area (Winkler et al., 2010). Similarly wide ranges can also be observed for

regional volumes and in developmental samples where the raw data are either reported or visualised. It is this degree of individual variability that makes longitudinal designs imperative for describing developmental trajectories. Articles that only report group averages or graph best-fitting models miss the opportunity to reveal this incredible diversity. Presenting the raw values of individual brain measurements is needed to convey the degree of overlap that can exist between groups and across development.

### 2.6.2 Intraindividual variability

How much can we reasonably expect an individual's brain structure to change? The answer to this question will depend on the age period studied, the time interval between scans, as well as what is being measured. Most longitudinal studies that describe the amount of structural change that has occurred over a period of time will do so only on a group level, and some of the few that report change across individuals are studies comparing developmental changes in brain structure with cognitive performance (Schnack et al., 2014; Tamnes, Walhovd, Grydeland, et al., 2013; Vijayakumar et al., 2013). These studies reveal substantial individual variability in change in certain brain structures across development. However, studies that correlate developmental changes in brain structure with developmental changes in cognitive performance are unable to quantify what amount of structural change is due to developmental events unrelated to cognitive capacities. However, it might be that we will never be able to fully disentangle these factors. One recent functional MRI study has gone further than reporting individuals differences in rates of change by comparing individual differences in longitudinal growth curves with performance on an inhibitory control task (Ordaz, Foran, Velanova, & Luna, 2013). This technique

(extensively described in their methods section) will become more feasible for future investigations as datasets grow larger and gain more waves of data.

### 2.6.3 Considerations for large datasets

Longitudinal studies are costly, and often involve the collection of large amounts of non-imaging data to relate to brain measures. These rich datasets have the capability to describe how brain development relates to biological measures such as genes, hormones, and prenatal measurements, as well as to measures of behaviour, cognitive development, and well-being. However, the large number of possible tests that could be run in large datasets make them vulnerable to practices that could bias our knowledge (Ioannidis, Munafò, Fusar-Poli, Nosek, & David, 2014). It is possible to guard against this possibility by reporting all tests that were conducted, including tests that failed to find a relationships between measures (Simmons, Nelson, & Simonsohn, 2011). Researchers in epidemiology have emphasised the need for specific hypotheses even in large datasets: "Developing large national cohorts without attention to specific hypotheses is inefficient, will fail to address many associations with high quality data, and may well produce spurious results" (Kuller, Bracken, Ogino, Prentice, & Tracy, 2013). It is therefore important for future studies to make transparent which tests are exploratory, and which are hypothesis driven (Miguel et al., 2014).

## 2.7 Conclusion

This chapter has highlighted a number of potential issues and choices that researchers examining structural brain development using longitudinal designs might encounter. Choices in regard to measurements, processing, analysis and

modelling may affect results and interpretations of longitudinal brain imaging studies.

## 3.1 Introduction

Comparative studies of brain development are often confronted with the question of controlling for overall head size between participants. Controlling for head size, or intracranial volume (ICV), can affect the results of a study, and this is an important consideration for studies describing changes in brain structure across development, or studies comparing groups (e.g., females vs. males, clinical groups vs. controls). The present study used longitudinal structural magnetic resonance imaging (MRI) to i) characterise how ICV changes between childhood and adulthood, ii) describe the physical development correlates for such changes, and iii) demonstrate how controlling for ICV (either by adding it as a covariate or dividing a measure by ICV) could impact investigations of brain development.

There are currently no longitudinal studies examining how ICV develops between childhood and adulthood. This is likely because it is generally assumed that ICV matures by late childhood, as was the conclusion from the first study to characterise ICV development *in vivo* (Pfefferbaum et al., 1994). Pfefferbaum and colleagues (1994) examined the ICV of 88 individuals aged 3 months to 30 years in the first cross-sectional study of its kind. Their results showed an increase in ICV between infancy and age 10 years, with ICV appearing roughly stable between ages 10 and 30 years (Pfefferbaum et al., 1994). However, a later study of 116 individuals aged 19 months to 80 years showed an increase in ICV between ages 2 and 14 years, with ICV appearing roughly stable between ages 16 and 80 years (Courchesne et al., 2000). Both studies reported that, on average, female participants had smaller ICV than male participants. Courchesne et al.

(2000) reported ICV was around 10% smaller for females than males across all ages. However, both of these studies relied on cross-sectional estimates, which limits the accuracy to which either could estimate the developmental trajectory of ICV between childhood and adulthood. The aim of the first analysis of this chapter was to characterise how ICV develops between childhood and adulthood using a longitudinal sample of structural MRI data.

As discussed in Chapter 2, most studies investigating developmental brain changes compare brain measures to age. However, changes that occur with age are just one way in which we can describe the development of a brain structure. As many physical changes are occurring between late childhood and across adolescence, such as a growth spurt in height, simply comparing brain development to age confounds what developmental processes most closely relate to observed brain changes. By investigating what physical developmental changes best relate to changes in brain measures, we glean a better understanding of possible underlying mechanisms. For example, if changes in certain brain measures occur in tandem with pubertal development, it would be reasonable to hypothesise that pubertal hormones play some role in the development of these brain measures. The aim of the second analysis of this chapter was to describe what aspects of physical development are most closely related to ICV development.

As certain brain structures scale with ICV, brain imaging researchers will sometimes correct brain measures for ICV in order to obtain a relative measure of the structure (Sanfilipo, Benedict, Zivadinov, & Bakshi, 2004). Obtaining a relative measure of the brain structure of interest allows the researcher to infer

that the differences between participants (or across time) are not due to differences in overall cranial size, but instead reflect differences in the specific structure of interest. As some brain measures do not scale with ICV (such as cortical thickness), it is not necessary to correct for ICV in all studies of brain structure. Some developmental studies have opted not to adjust brain volumes for ICV (e.g., Goddings et al., 2013), because it is still unclear how doing so could affect results in longitudinal developmental investigations. Indeed, the developmental trajectories of the brain structures examined in this recent paper were largely distinct, calling into question the advantage of controlling for ICV in studies of longitudinal brain development (Goddings et al., 2013).

Controlling for ICV has been recommended for longitudinal studies of structural brain measures under the assumption that brain volumes are more comparable after they have been corrected by ICV (Whitwell, Crum, Watt, & Fox, 2001). However, the only studies that have assessed how correcting for ICV affects longitudinal brain measures have examined changes that occur in old age. It might be that developmental processes underlying changes in ICV are affected differently by ICV correction than changes that occur in late life. This is why it is imperative not only to characterise the shape of age-related changes ICV between childhood and adulthood, but also to understand what physical developmental changes and characteristics are related to ICV development. Finally, it is important to understand how controlling for ICV could impact on developmental models of brain measures. As previous evidence suggests that, on average, ICV is smaller in females than in males, it is possible that controlling for ICV will affect the perceived influence of gender in models of brain development. The aim of the present study is to address these concerns.

The three hypotheses of the present study are as follows:

1. ICV will show a significant change between late childhood and early adulthood.
2. Measures of physical development will describe ICV development better than age during this period.
3. Controlling for ICV will affect brain developmental trajectories, reducing reported gender differences.

## 3.2 Methods

### 3.2.1 Participants

The sample consisted of 33 individuals (ages 7–30 years; 10 females), each of whom had undergone at least three structural MRI sessions (136 scans total; Figure 3.1). These participants were selected from the NIMH Child Psychiatry Branch study of neurotypical brain development for having fulfilled the criteria of having i) at least three high quality MRI scans spanning between late childhood and late adolescence, and ii) complete data on their physical development (height, weight, and pubertal status) at each time point. Participants were recruited from the community through local advertisement and were paid for their participation in the study. The institutional review board of the National Institutes of Health approved the research protocol employed in this study and written informed consent and assent to participate in the study were obtained from parents/adult participants and children respectively.

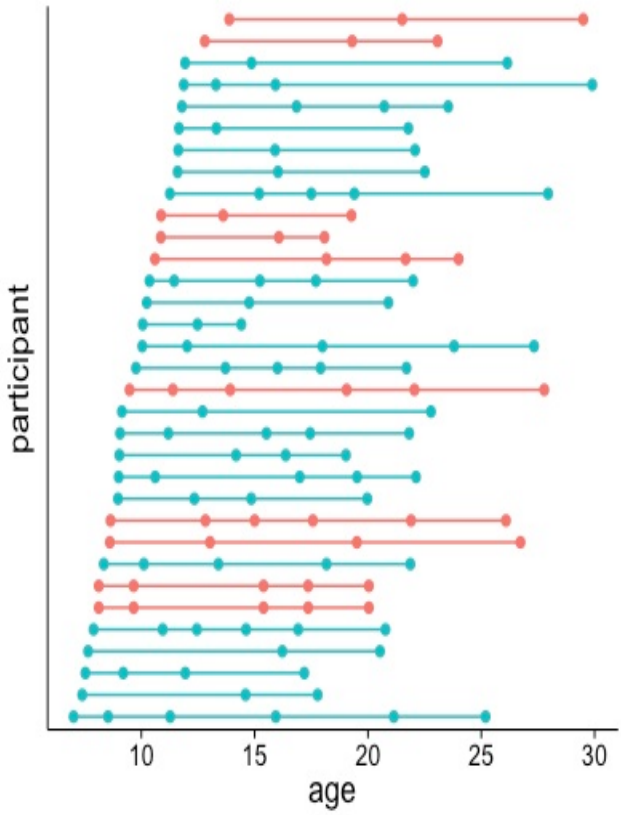


**Figure 3.1. Age distribution of the sample.** The age at each scan is indicated by a filled circle. Each participant is represented by one line, connecting all the time points in which they have a scan in the present sample. Females are represented in red, and males are represented in blue.

Two individuals were monozygotic twins, and two pairs of individuals were siblings. Demographic characteristics were measured for each participant at the time of her or his first scan (see Table 3.1). These characteristics included ethnicity, socioeconomic status (using Hollingshead scales; Hollingshead, 1975), IQ (using age-appropriate Wechsler Intelligence Scales; Wechsler, 1999) and handedness (using Physical and Neurological Examination of Soft Signs inventory; Denckla, 1984). The IQs of participants in the sample ranged from 99–139 (mean IQ 117.6 ± 10.5). There were no significant differences between females and males in handedness, ethnicity, IQ, socioeconomic status (SES), or number of scans. The absence of neurological or psychiatric disorder was established through completion of a screening questionnaire (Childhood Behaviour Checklist; Achenbach & Edelbrock, 1991) at each time point.

| Characteristic | Group All | Female | Male | Sex Difference |
|---|---|---|---|---|
| Number of individuals | 33 | 10 | 23 | $p < 0.03$ |
| Singleton | 31 | 8 | 23 | |
| Member of twin pair | 2 | 2 | 0 | |
| Handedness | | | | n.s. |
| Right | 33 | 10 | 23 | |
| Mixed | 0 | 0 | 0 | |
| Left | 0 | 0 | 0 | |
| Ethnicity | | | | n.s. |
| Caucasian | 29 | 9 | 20 | |
| African-American | 2 | 0 | 2 | |
| Asian | 2 | 1 | 1 | |
| Hispanic | 0 | 0 | 0 | |
| Other | 0 | 0 | 0 | |
| IQ | | | | n.s. |
| Mean (SD) | 117.6 (10.5) | 114.6 (12.1) | 118.8 (9.8) | |
| SES | | | | n.s. |
| Mean (SD) | 33.5 (16.1) | 37.2 (10.3) | 31.8 (18.0) | |
| Number of scans | | | | n.s. |
| 2 scans | 0 | 0 | 0 | |
| 3 scans | 13 | 4 | 9 | |
| 4 scans | 7 | 2 | 5 | |
| 5 scans | 9 | 2 | 7 | |
| 6 scans | 4 | 2 | 2 | |
| 7 scans | 0 | 0 | 0 | |
| Total | 136 | 42 | 94 | |
| Age Distribution of Scans (years) | | | | n.s. |
| Mean (SD) | 15.8 (5.5) | 16.6 (5.8) | 15.4 (5.3) | |
| Range | 7.0-29.9 | 8.1-29.5 | 7.0-29.9 | |

n.s., not statistically significant at $p < 0.05$; SES, socioeconomic status.

**Table 3.1. Participant demographics.** There were 33 participants (10 female, 23 male). Genders did not differ in handedness, ethnicity, IQ, SES, number of scans, or age distribution of scans.

### 3.2.2 Measures of interest

Measures of physical development (height, weight, pubertal stage and age) were measured at each time point (Table 3.2). Pubertal stage was estimated using Tanner stage diagrams, which include drawings of stages of breast/genital and pubic hair growth (Taylor et al., 2001). For the purposes of obtaining one measure of pubertal stage at each time of measurement, a single combined Tanner stage score (range: 1 to 5, with 1 representing pre-pubertal and 5 representing pubertal completion) was assigned based on the overall stage that the participant felt best

described herself/himself. Across the data points, male participants were on average taller than female participants ($p$ = 0.047), but pubertal stage, age, and weight did not significantly differ between females and males.

| Characteristic | Group All | Female | Male | Sex Difference |
|---|---|---|---|---|
| Number of individuals | 33 | 10 | 23 | p < 0.03 |
| Pubertal Stage | 3.5 (1.6) | 3.8 (1.6) | 3.4 (1.6) | n.s. |
| Height | 63.7 (7.1) | 61.5 (5.5) | 64.7 (7.5) | p = .047 |
| Weight | 129.3 (47.3) | 120.9 (35.6) | 133.1 (51.4) | n.s. |
| Age | 15.8 (5.5) | 16.6 (5.8) | 15.4 (5.3) | n.s. |
| n.s., not statistically significant at p < 0.05 | | | | |

**Table 3.2. Developmental measures of interest (non-brain).** Genders did not differ in pubertal stage, weight, or age. Males were taller than females on average ($p$ = .047). Measures were averaged across all available time points.

A measure of ICV was acquired for each participant at each structural MRI scan. In addition, a measure of cortical grey matter volume was also obtained to assess how correcting for ICV could affect the results of a developmental assessment of brain measures. The details of the brain imaging acquisition and processing procedure are detailed in the following sections.

### 3.2.3 Image acquisition

All MRI scans were T-1 weighted images with contiguous 1.5 mm axial slices and 2.0 mm coronal slices, obtained on the same 1.5-T General Electric Signa scanner (Milwaukee, WI) using a 3D spoiled gradient recalled echo sequence with the following parameters: echo time 5 ms; repetition time 24 ms; flip angle 45° (degree); acquisition matrix 256 × 192; number of excitations 1; and field of view 24 cm. A clinical neuroradiologist evaluated all scans for gross abnormalities.

### 3.2.4 Image processing

Cortical reconstruction was performed with the FreeSurfer image analysis suite (version 5.3), which is documented and freely available online

(http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in detail in seminal publications (e.g., Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999). This processing stream for structural magnetic resonance images includes motion correction (Reuter, Rosas, & Fischl, 2010), removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Ségonne et al., 2004), automated Talairach transformation, intensity normalisation (Sled, Zijdenbos, & Evans, 1998), tessellation of the grey matter white matter boundary, automated topology correction (Fischl, Liu, & Dale, 2001; Ségonne, Pacheco, & Fischl, 2007), and surface deformation following intensity gradients to optimally place the grey/white and grey/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale et al., 1999; Dale & Sereno, 1993; Fischl & Dale, 2000). Each cortical model was registered to a spherical atlas using individual cortical folding patterns to match cortical geometry across participants (Dale et al., 1999).

To extract reliable estimates for cortical grey matter volume, images were processed using FreeSurfer 5.3's longitudinal stream (Reuter et al., 2012). This process includes the creation of an unbiased within-subject template space and image using robust, inverse consistent registration (Reuter et al., 2010). Several processing steps, such as skull stripping, Talairach transforms, atlas registration as well as spherical surface maps and parcellations are then initialised with common information from the within-subject template, significantly increasing reliability and statistical power (Reuter et al., 2012). All images were visually inspected post-processing for accuracy.

Cortical grey matter volume ($mm^3$) was measured using the surface-based reconstructed image. As FreeSurfer 5.3's longitudinal pipeline assumes a constant ICV, the ICV measures were extracted from each scan after being processed through the cross-sectional pipeline, but before being processed through the longitudinal pipeline. Since ICV correlates with the determinant of the transform matrix used to align an image with an atlas, FreeSurfer uses an atlas based spatial normalisation procedure to estimate ICV (Buckner et al., 2004).

### 3.2.5 Analysis procedure

Three separate analyses were conducted to address the three aims of the present study.

The aim of the first analysis was to characterise how ICV changes across development in a longitudinal sample. For this analysis I used mixed-effects modelling (R version 3.1-102; nlme package). This method allows an estimation of the fixed effects of measured variables on volume change, while incorporating the longitudinal nature of the data by including within-person variation as nested random effects. The following models were tested:

1. Linear model: ICV = Intercept + $\alpha$(age)
2. Quadratic model: ICV = Intercept + $\alpha$(age) + $\beta(age^2)$
3. Cubic model: ICV = Intercept + $\alpha$(age) + $\beta(age^2)$ + $\gamma(age^3)$

Where $\alpha$, $\beta$, and $\gamma$ represent the constant terms defining the effects of each fixed term. Models where the marginal p-value of the highest order variable was significant ($p < 0.05$) were then compared to determine which was the best fit, as determined by Akaike Information Criterion (AIC). Unless stated otherwise, all p-values reported in the main text were obtained by likelihood ratio tests comparing

the best fitting model against a baseline (null) model that includes only the random effects and not the fixed effects of interest.

The aim of the second analysis was to test if changes in physical development (pubertal stage, height and weight) could describe the development of ICV above and beyond age. This analysis was similar to the first, in that I first tested linear, quadratic, and cubic models for each of the physical developmental measures of interest (pubertal stage, height, and weight). However, in addition to assessing the best models for each physical measure of interest, I also performed an automated model selection procedure (MuMIn1.9.0 package; Barton, 2013) on a global model that included all variables of interest: age, gender, pubertal stage, height, and weight. This automated model selection procedure assesses all possible combinations of variables to determine, using the Second-order Akaike Information Criterion (AICc; Burnham & Anderson, 2002), one best fitting "multi-variable" model. This multi-variable model was then compared against the best fitting single-variable models using AIC and likelihood ratio tests.

The aim of the third analysis was to examine how controlling for ICV could impact investigations of brain development. To do so, I investigated how controlling for ICV changes the best fitting age model for cortical grey matter volume. First, I assessed the best fitting age model for cortical grey matter volume using the same procedure described in for ICV in the first analysis. As gender is often included in models of brain development, and given the relationship between ICV and gender, I then tested to see if adding gender improved the best fitting age model. Two different methods of controlling for ICV were then tested in this analysis: the covariate method and correction method. To test the covariate

method, I included ICV as a variable in the best fitting age model (including gender if appropriate). I then used the automated selection procedure described in the second analysis to see if the best fitting model (as selected by this automated procedure) still included the same variables as before, and/or the ICV variable. I also compared the best fitting age model with ICV against the best fitting age model with ICV using AIC and likelihood ratio tests. To test the correction method, cortical grey matter volume was divided by ICV for each participant at each time point. I then assessed the best fitting age model for adjusted cortical grey matter volume using the same procedure described for the covariate method: i) test for best age model; ii) test if gender improves the model fit.

## 3.3 Results

### 3.3.1 ICV continues to change between late childhood and early adulthood

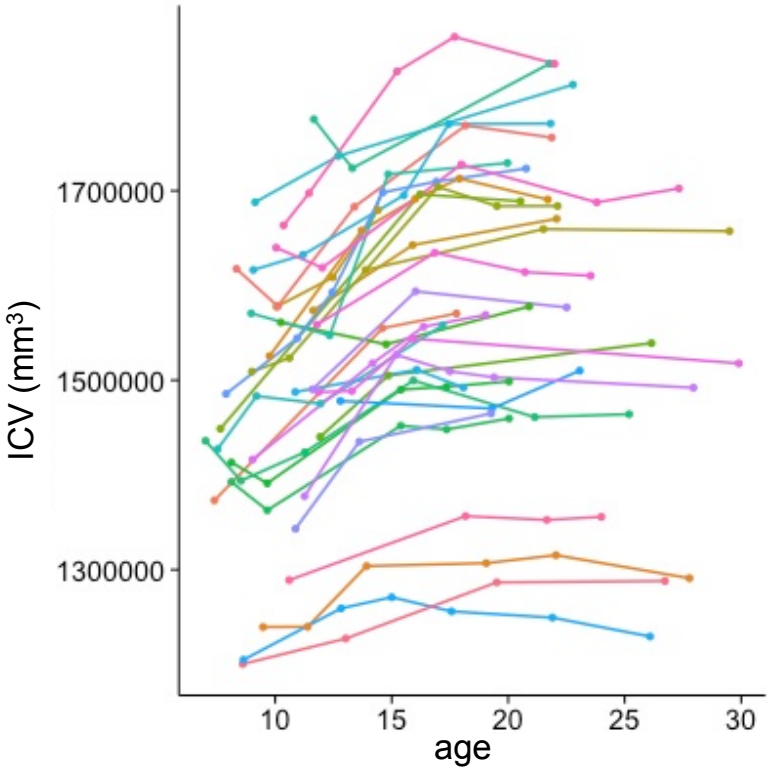


**Figure 3.2. Changes in ICV across development.** Each line represents one participant, and each filled circle represents one time point. Age in years is measured along the x-axis and ICV ($mm^3$) is along the y-axis.

As pictured in Figure 3.2, ICV varies not only between individuals (cross-sectional sample range: 1,200,413mm$^3$ – 1,862,496mm$^3$), but also within individuals across time. Of the three models tested (see Table 3.3), the best fitting age model for ICV was a quadratic trajectory (LR = 126.6, $p < 0.0001$; Table 3.4). Based on the population model for this sample, ICV appears to increase around 12% on average from late childhood until the early twenties (Figure 3.3). The results of this analysis supported the hypothesis that ICV will show a significant change between late childhood and early adulthood.

| | Model | df | AIC | BIC | logLik | Test | L.Ratio | p-value |
|---|---|---|---|---|---|---|---|---|
| Null Model | 1 | 3 | 3499 | 3507 | -1746 | | | |
| Linear Age Model | 2 | 4 | 3434 | 3445 | -1713 | 1 vs 2 | 66.9 | <.0001 |
| Quadratic Age Model | 3 | 5 | 3376 | 3391 | -1683 | 2 vs 3 | 59.8 | <.0001 |
| Cubic Age Model | 4 | 6 | 3378 | 3395 | -1683 | 3 vs 4 | 0.05 | 0.82 |

**Table 3.3. Model comparison table for ICV.** Linear (model 2), quadratic (model 3), and cubic (model 4) age models were compared to each other and the baseline (null; model 1) model. While the linear model was a significantly better fit than the null model, the quadratic model was a significantly better fit than the linear model, despite having more degrees of freedom. The cubic model, while a better fit than the linear model, was not significantly better than the quadratic model. df: degrees of freedom; AIC: Akaike information criterion; BIC: Bayesian information criterion; logLik: log likelihood; L.Ratio: likelihood ratio.

| | Model | df | AIC | BIC | logLik | Test | L.Ratio | p-value |
|---|---|---|---|---|---|---|---|---|
| Null Model | 1 | 3 | 3499 | 3507 | -1746 | | | |
| Quadratic Age Model | 2 | 5 | 3376 | 3391 | -1683 | 1 vs 2 | 126.6 | <.0001 |

**Table 3.4. Quadratic age model compared to baseline.** This table compares the best fitting age model for ICV (quadratic) to the baseline (null) model. df: degrees of freedom; AIC: Akaike information criterion; BIC: Bayesian information criterion; logLik: log likelihood; L.Ratio: likelihood ratio.

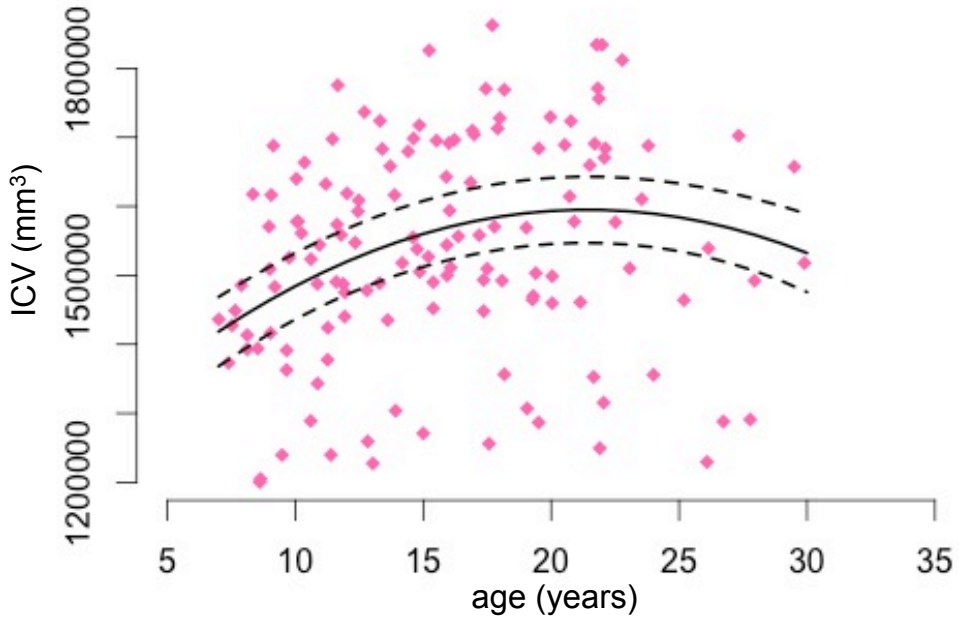


**Figure 3.3. Best fitting age model for ICV in present sample.** The best fitting model is represented by the solid black line. Dashed lines represent 95% confidence internals. Each pink diamond represents one scan. Age in years is measured along the x-axis and ICV ($mm^3$) along the y-axis.

### 3.3.2 ICV development is related to physical development

Of the three model shapes (linear, quadratic and cubic) tested against ICV, a cubic model was the best fit for pubertal stage (LR = 123.0, $p < 0.0001$), a quadratic model was the best fit for height (LR = 168.4, $p < 0.0001$), and a cubic model was the best fit for weight (LR = 141.1, $p < 0.0001$). The best fitting multi-variable model included height, gender, and pubertal stage (LR = 193.6, $p < 0.0001$). The multi-variable model was a better fit than any of the single variable models (Table 3.5). The results of this analysis supported the hypothesis that physical development will describe ICV development better than age between late childhood and early adulthood.

| | Model | df | AIC | BIC | logLik |
|---|---|---|---|---|---|
| Null Model | 1 | 3 | 3498.6 | 3507.3 | -1746.3 |
| Best Age Model | 2 | 5 | 3375.9 | 3390.5 | -1683.0 |
| Best Pubertal Model | 3 | 6 | 3381.6 | 3399.0 | -1684.8 |
| Best Height Model | 4 | 5 | 3334.1 | 3348.7 | -1662.1 |
| Best Weight Model | 5 | 6 | 3363.5 | 3380.9 | -1675.7 |
| Best Multi-variable Model | 6 | 9 | 3316.9 | 3343.1 | -1649.5 |

**Table 3.5. Best fitting models for ICV in present sample.** This table displays the best fitting models for each single variable of interest (linear, quadratic or cubic), as well as the best fitting multi-variable model (highlighted to indicate the best fit of all models). df: degrees of freedom; AIC: Akaike information criterion; BIC: Bayesian information criterion; logLik: log likelihood.

### 3.3.3 Controlling for ICV affects brain developmental trajectories

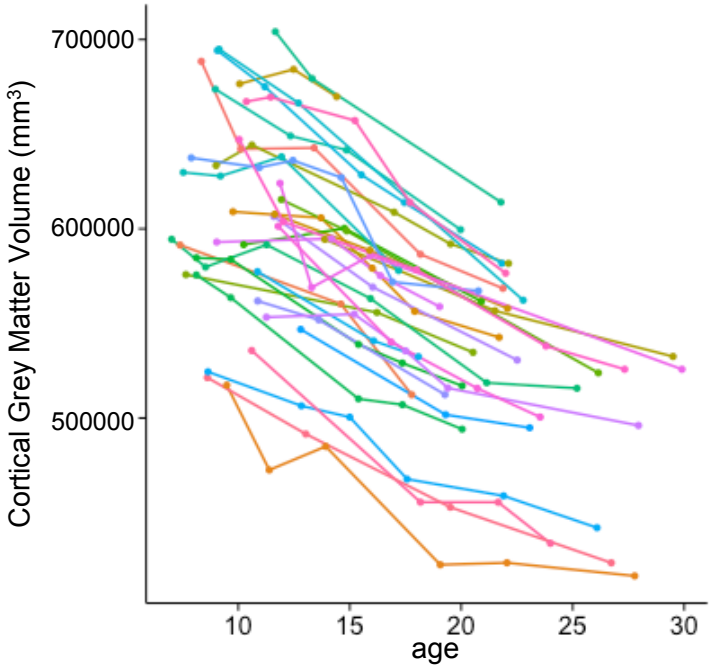


**Figure 3.4. Changes in cortical grey matter volume across development.** Each line represents one participant, and each filled circle represents one time point. Age in years is measured along the x-axis and cortical grey matter volume ($mm^3$) is along the y-axis.

The best fitting age model for cortical grey matter volume was a cubic trajectory (LR = 231.0, $p < 0.0001$), and adding gender as a main effect significantly improved the model fit (cubic age model vs. cubic age model with gender: LR =

23.6, $p < 0.0001$). The raw plots for cortical grey matter volume are displayed in Figure 3.4.

*The covariate method:* Adding ICV as a covariate to this model significantly improved the model fit (cubic age model with gender vs. cubic age model with gender and ICV: LR = 16.7, $p < 0.0001$). Table 3.6 displays all tested models.

| | Model | df | AIC | BIC | logLik | Test | L.Ratio | p-value |
|---|---|---|---|---|---|---|---|---|
| Null Model | 1 | 3 | 3324.0 | 3332.7 | -1659.0 | | | |
| Cubic Age Model | 2 | 6 | 3098.9 | 3116.4 | -1543.5 | 1 vs 2 | 231.1 | <.0001 |
| Cubic Age Model + Gender | 3 | 7 | 3077.4 | 3097.7 | -1531.7 | 2 vs 3 | 23.6 | <.0001 |
| Cubic Age Model + ICV | 4 | 7 | 3078.0 | 3098.4 | -1532.0 | | | |
| Cubic Age Model + Gender + ICV | 5 | 8 | 3062.6 | 3085.9 | -1523.3 | 4 vs 5 | 17.4 | <.0001 |

**Table 3.6. Model fits for cortical grey matter volume.** This table displays the best fitting age model for cortical grey matter volume (cubic; model 2), the cubic age model with gender added (model 3), the cubic age model with ICV added (model 4), the cubic model with both gender and ICV added (model 5), and the baseline (null) model (model 1). Model 5 is highlighted as it is the best fitting model of the four. df: degrees of freedom; AIC: Akaike information criterion; BIC: Bayesian information criterion; logLik: log likelihood; L.Ratio: likelihood ratio.

*The correction method:* The raw plots for adjusted cortical grey matter volume are displayed in Figure 3.5. Similar to unadjusted cortical grey matter volume, the best fitting age model for adjusted cortical grey matter volume was a cubic trajectory (LR = 291.3, $p < 0.0001$). However, when cortical grey matter volume is adjusted by ICV, adding gender as a main effect no longer improves the model fit ($p = 0.95$). The results of this analysis supported the hypothesis that controlling for ICV will affect brain developmental trajectories, and possibly reduce reported gender differences.

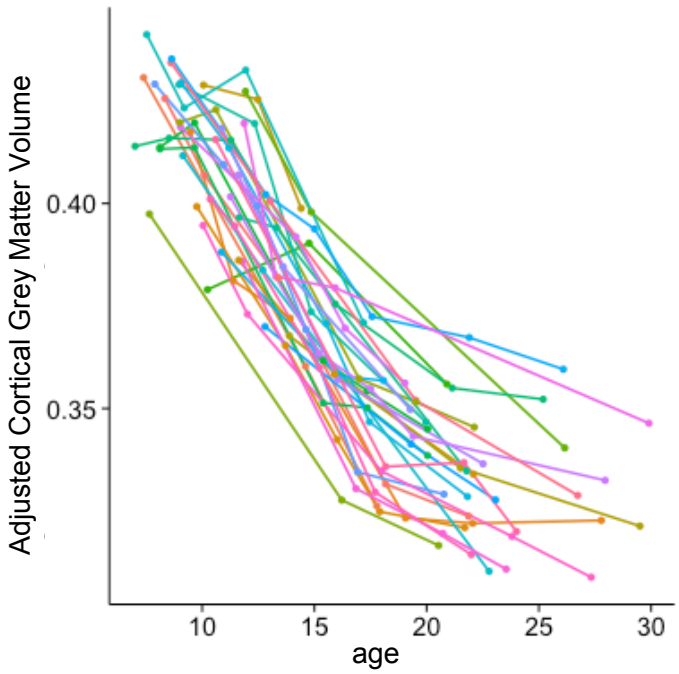


**Figure 3.5. Adjusted cortical grey matter volume across development.** Each line represents one participant, and each filled circle represents one time point. Age in years is measured along the x-axis and adjusted cortical grey matter volume (cortical grey matter volume divided by ICV) is along the y-axis.

## 3.4 Discussion

This study examined how intracranial volume (ICV) develops between late childhood and early adulthood, the physical processes that are associated with this development, and how correcting for ICV could impact developmental studies. The results showed that ICV increases by ~12% between late childhood and early adulthood. Furthermore, the development of ICV during this time was related more to the physical characteristics height, pubertal status and gender, rather than age. Finally, these results suggest that the method in which one controls for ICV could impact the perceived impact of gender on brain developmental trajectories.

The present study extends previous work charting the development of ICV by providing the first longitudinal evidence for the continued development of ICV through adolescence. In this sample of 33 participants scanned at least three times

between late childhood and early adulthood (sample range: 7–30 years), the best fitting population age model was quadratic, with ICV showing an increase until the late teens. The raw data for each participant showed variability between participants with an overall trend for increasing ICV until the middle teen years. The result of the first analysis of the present study, which suggests a relatively protracted development of the ICV throughout the teen years, is in contrast to the results of previous cross-sectional studies of ICV development. These previous studies suggested that ICV was finished developing by age 10 years (Pfefferbaum et al., 1994), or by roughly age 14 years (Courchesne et al., 2000). It is likely that the relatively small sample sizes spanning large age ranges (from infancy to adulthood) of these studies, as well as their cross-sectional design, limited the ability for these studies to detect subtleties in ICV development beyond the gross changes occurring between infancy and early adolescence.

The transition between late childhood and adolescence is accompanied by significant changes in physical characteristics such as height and weight, as well as the multitude physical and hormonal changes associated with puberty. Similar to age, non-linear changes in these physical developmental measures could significantly model changes in ICV in the present sample. Indeed, a quadratic height model was a better fitting model than a quadratic age model, suggesting that ICV development is more closely related to this measure of physical development than it is to the most commonly used developmental measure, age. However, the best fitting model to describe ICV development included the physical characteristics height, puberty, and gender. This result suggests that the underlying processes associated with the late childhood growth spurt in height, as well as the pubertal transition across adolescence, are also related to changes in

ICV during this period of development. The inclusion of gender in the model, which improved the model fit, suggests that factors associated with gender, above and beyond differences in height and pubertal development, could influence ICV development. In addition, the exclusion of age and weight from the best fitting multi-variable model suggests that these two factors did not add any significant explanatory weight to the population developmental model of ICV for this sample.

The results of this study have implications for studies of structural brain development between late childhood and early adulthood. There is currently no consensus as to whether it is necessary to adjust brain volumes by ICV or whole brain volume in longitudinal studies of brain development, with some studies choosing to do so (Dennison et al., 2013; Urošević, Collins, Muetzel, Lim, & Luciana, 2012), and some studies opting to analyse the raw volumes of brain structures (Goddings et al., 2013; Wierenga, Langen, Ambrosino, et al., 2014). In this study, I assessed how population age models for cortical grey matter volume could be affected by controlling for ICV. To do so, I assessed two methods of controlling for ICV: the first method included ICV as a covariate in the model for cortical grey matter volume, and the second method divided cortical grey matter volume by ICV. Before controlling for ICV, cortical grey matter volume followed a cubic trajectory, decreasing in volume through the second decade into the early twenties. While both methods of controlling for ICV did not affect the type of best fitting population age model for cortical grey matter volume (it remained a cubic model), dividing cortical grey matter volume by ICV did appear to affect the perceived level of change that occurs across development in this sample (see Figures 3.4 and 3.5). As ICV increases into the mid-teen years before stabilising,

and cortical grey matter shows a roughly steady decrease in volume through the second decade, these two changes interact with one another in such a way that it appears that cortical grey matter volume sharply declines between late childhood and the mid-teen years. Based on this result, it could be assumed that the specific shape of ICV development has an impact on the developmental trajectories of brain volumes that have been adjusted by ICV. As brain structures, such as subcortical volumes, have been shown to follow a variety of developmental trajectory shapes (Goddings et al., 2013), adjusting for ICV could have a large impact on the interpretation of brain developmental patterns.

In addition to demonstrating how controlling for ICV could affect the trajectory of population age models, this study assessed how controlling for ICV affected the perceived influence of gender on cortical grey matter development. The results of this study suggest that the method in which one controls for ICV could affect the perceived influence of gender on cortical grey matter development. Specifically, when ICV was added as a covariate, the best fitting model for cortical grey matter volume still included gender. However, when cortical grey matter volume was divided by ICV, gender was no longer included in the best fitting model. The covariate method therefore suggests that gender influences cortical grey matter volume development in a way that cannot be explained by gender differences in ICV, whereas the adjustment method suggests that gender differences in the development of cortical grey matter volume can be explained by gender differences in ICV. These two conflicting interpretations illustrate how methodological differences can impact on our understanding of brain development. As the role of gender in brain development is contentious, with some arguing that population-level gender differences in brain structure are due to

population-level gender differences in physical size (see discussion in Chapter 2), it is important to understand the relationship between covariates and gender in analyses of brain structure.

Overall, this study contributes to our understanding of how a non-brain measure, ICV, could impact on studies of structural brain development. Future work is needed to see if the results found in this sample replicate in other samples, including samples that cover different age ranges. In addition, as some studies of structural brain development control for whole brain volume rather than ICV, it would be informative to repeat the three analyses conducted in the present study for whole brain volume.

## 3.5 Conclusion

Based on the results of the present study, it seems feasible to suggest that longitudinal investigations with the aim of characterising the developmental trajectories of brain volumes should not correct their volumes for individual differences in ICV. This is because ICV is changing substantially throughout adolescence, and correcting for this specific pattern of development could skew the shape and perceived magnitude of changes in brain volume in longitudinal studies. Therefore, I have conducted any subsequent analyses of volumetric brain development in this thesis using raw measurements of brain volume. However, this conclusion pertains only to longitudinal studies, as it might still be relevant for cross-sectional studies to adjust for ICV when conducting structural brain imaging analyses in developing samples.

# Chapter 4 The developmental mismatch in structural brain maturation during adolescence

## 4.1 Introduction

The developmental mismatch hypothesis proposes that, in humans, subcortical structures involved in processing affect and reward develop (mature) earlier than cortical structures involved in cognitive control, and that this mismatch in maturational timing is most exaggerated during adolescence (Casey, Getz, & Galvan, 2008; Somerville, Jones, & Casey, 2010; Steinberg, 2008). Furthermore, the mismatch in maturational timing between these two systems has been proposed to underlie stereotypical adolescent behaviours such as risk taking, sensation seeking and heightened emotional reactivity. Despite the popularity of this model (see Table 4.1), previous studies have not directly assessed the relative maturational timing of the two systems longitudinally within the same individuals, and have not established whether the developmental mismatch between these systems relates to the risk-taking and sensation-seeking behaviours of an individual during adolescence. The present study used a longitudinal sample of structural MRI scans to test the developmental mismatch hypothesis at both group- and individual-levels, and related individual differences in brain maturation to retrospectively self-reported risk-taking and sensation-seeking behaviour during adolescence.

| Study | amygdala | NAcc | dlPFC | dACC | vmPFC | OFC | Age groups | Process | Task |
|---|---|---|---|---|---|---|---|---|---|
| Bjork et al., 2004 | | VS | | | | | 12 adolescents (12-17 years);<br>12 adults (22-28 years) | Reward anticipation of gains versus non-gains | Monetary Incentive Delay task |
| Ernst et al., 2005 | amygdala | NAcc | | | | | 16 adolescents (9-17 years);<br>14 adults (20-40 years) | Response to reward outcome feedback | Wheel of fortune task |
| Galvan et al., 2006 | | NAcc* | | | | OFC | 13 children (7-11 years);<br>12 adolescents (13-17 years);<br>12 adults (23-29 years) | Reward anticipation and response to outcome feedback | Pirate reward paradigm |
| Eshel et al., 2007 | | | dlPFC | dACC | | OFC/vlPFC | **Same sample as Ernst et al., 2005** | Risky decision making | Wheel of fortune task |
| Hare et al., 2008 | amygdala* | | | | | | 11 children (7-12 years);<br>24 adolescents (13-18 years);<br>24 adults (19-32 years) | Response to target/non-target emotional faces | Go/no-go with emotional faces |
| Van Leijenhorst et al., 2010a | | VS* | | | | OFC | 17 young adolescents (10-12 years);<br>18 mid-adolescents (14-15 years);<br>15 adults (18-23 years) | Response to passive reward outcome feedback | Slot machine task |
| Van Leijenhorst et al., 2010b | | VS | dlPFC | dACC | vmPFC* | medial OFC* | 12 pre-pubertal children (8-10 years);<br>15 pubertal adolescents (12-14 years);<br>15 post-pubertal adolescents (16-17 years);<br>15 adults (19-26 years) | Risky decision making | Cake gambling task |
| Van Leijenhorst et al., 2010b | | VS* | dlPFC | dACC | vmPFC | | | Response to reward outcome feedback | Cake gambling task |
| Geier et al., 2010 | | VS | | ACC/ MFG | | | 18 adolescents (13-17 years);<br>16 adults (18-30 years) | Reward anticipation | Monetary incentive-mediated anti-saccade |
| Somerville et al., 2011 | | VS* | | | | | 18 children (6-12 years);<br>19 adolescents (13-17 years);<br>25 adults (18-29 years) | Response to target/non-target emotional faces | Go/no-go with emotional faces |
| **Key** | | | | | | | | | |
| BOLD signal magnitude | greater during childhood | | | greater during adolescence | | | greater during adulthood | no difference | * peak during adolescence |

**Table 4.1**. This table describes the findings from 10 studies that have investigated developmental changes (with an adult comparison group) in brain activity associated with reward-processing, risk-taking behaviour or emotional reactivity. dlPFC = Dorsolateral PFC; vlPFC = ventrolateral PFC; dACC = dorsal anterior cingulate cortex; VS = ventral striatum; MFG = middle frontal gyrus. I have outlined the developmental change reported in areas of the brain relevant to the developmental mismatch hypothesis: amygdala, NAcc, dorsolateral PFC, dorsal anterior cingulate cortex, vmPFC and OFC. If the study used different nomenclature for ROIs (e.g. VS), of which the NAcc is a major component, or reported a cluster that spanned more than the ROI (e.g. OFC/vlPFC), I use this nomenclature in the study's row. Developmental differences in BOLD signal magnitude for the process of interest are indicated by shading. An asterisk represents a peak in BOLD signal magnitude during adolescence.

### 4.1.1 The dual systems model of brain development

In a 2008 issue of Developmental Review, two influential reviews (Casey et al., 2008; Steinberg, 2008) proposed a dual systems model of brain development to account for the non-linear changes in behaviour observed between childhood and adulthood. In particular, the model sought to explain the changes in sensation-seeking and risk-taking behaviours that appeared to increase between childhood and adolescence, and subsequently decrease between adolescence and adulthood (Steinberg et al., 2008). Drawing from behavioural and neuroimaging studies, the dual systems model updated the previously held theory of development, which solely implicated the protracted development of the prefrontal cortex as underlying changes in cognitive control and impulse control across adolescence (Casey et al., 2008). Instead, the dual systems model proposed a more dynamic model incorporating the differential developmental timing of subcortical brain regions involved in processing affect and reward, and prefrontal cortical regions involved in cognitive control (Casey et al., 2008). The subcortical regions commonly implicated in this model include the ventral striatum or nucleus accumbens (NAcc) and amygdala (Somerville et al., 2010). The specific areas of the prefrontal cortex (PFC) implicated in this model include, but are not limited to, the dorsolateral prefrontal and dorsal anterior cingulate cortex (Steinberg, 2008). This developmental mismatch hypothesis posited that, in adolescence, relative maturity (i.e., earlier development) of subcortical regions compared to the prefrontal cortex allows for greater subcortical signaling, which is under-regulated by the prefrontal cortex (Casey et al., 2008; Somerville et al., 2010; Steinberg, 2008; Figure 4.1). During the developmental window when these subcortical regions are mature, but the prefrontal cortex is still developing, the salience of emotional contexts or possible rewards are proposed to be enhanced relative to in

adulthood, when the mature prefrontal cortex is better able to modulate the subcortical signals. Indeed, many cross-sectional functional neuroimaging studies have shown heightened activity in the NAcc in adolescents compared with other age groups during tasks that involve risky decision making, reward processing and emotion processing (Table 4.1; Bjork et al., 2004; Ernst et al., 2005; Eshel, Nelson, Blair, Pine, & Ernst, 2007; Galvan et al., 2006; Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010; Hare et al., 2008; Somerville, Hare, & Casey, 2011; Van Leijenhorst et al., 2010, 2010). The present study investigated whether the NAcc and amygdala display earlier structural maturity than the prefrontal cortex, as would be predicted by the dual systems model. This pattern of brain development is hence referred to as the developmental mismatch.

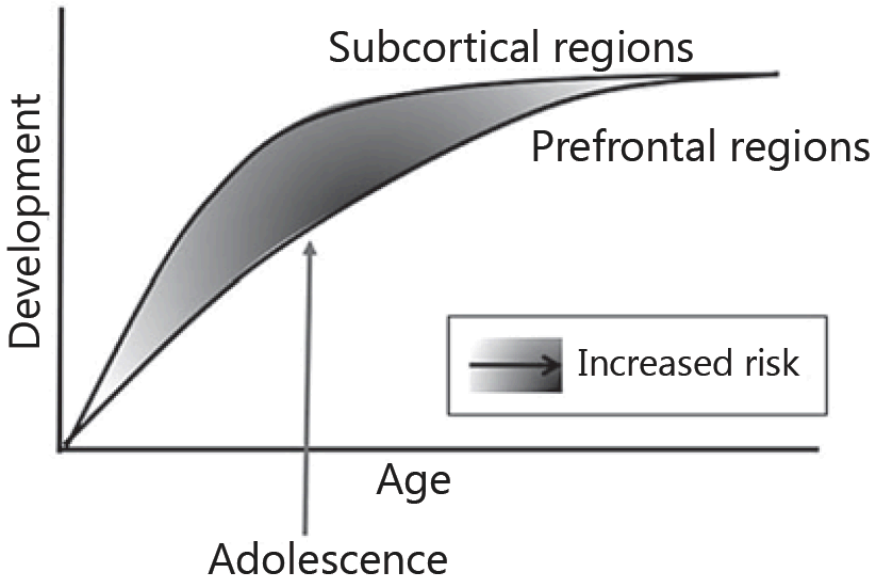


**Figure 4.1. The developmental mismatch model from Somerville et al. 2010.** This schematic model illustrates the proposed developmental mismatch in brain maturation, with subcortical regions (such as the amygdala and NAcc/ventral striatum) maturing during adolescence, whereas the PFC does not reach a similar level of maturity until adulthood. The authors hypothesised the gap (shaded) in maturity would increase the risk for affectively driven behaviours during adolescence.

### 4.1.2 Evidence from longitudinal studies of structural development

Previous longitudinal studies have reported inconsistent findings regarding the structural development of the amygdala and NAcc. In a longitudinal study of 85 individuals (170 scans) aged 8–22 years, the amygdala displayed little change in volume between childhood and adulthood, whereas the NAcc steadily decreased in volume around 0.6% annually between childhood and adulthood (Tamnes, Walhovd, Dale, et al., 2013). A previous study using the NIMH Child Psychiatry Branch sample involving 275 individuals (711 scans) found evidence for an increase in amygdala volume (approximately 7% between ages 7 and 20 years in females), with volumes stabilising during the later stages of puberty (Goddings et al., 2013). However, males in this sample showed a larger increase in amygdala volumes across this age range, which did not begin to stabilise until the late teens, when puberty had neared completion. The NAcc linearly decreased from ages 7–20 years in this sample for both males and females, losing approximately 8% of its volume across puberty (Goddings et al., 2013). In a longitudinal study of 60 adolescents (120 scans) between ages 12 and 16 years, the amygdala showed little change in volume, and the NAcc showed different developmental patterns by hemisphere, increasing in volume in the left hemisphere and decreasing in volume in the right hemisphere (Dennison et al., 2013). One of the few studies that has directly assessed the relationship between structural brain changes in adolescence with behaviour found non-linear development in the NAcc and no developmental changes for the amygdala (Urošević et al., 2012). In a sample of 184 individuals (341 scans) aged 9–23 years, the left NAcc appeared to show an increase from early adolescence to late adolescence, and an ~8% decrease from late adolescence to early adulthood (late teens to early 20s), whereas the right NAcc and bilateral amygdala did not show any age-related changes (Urošević et al., 2012). Reported positive affective responses to rewards were highest in late adolescence,

decreasing into young adulthood in a developmental pattern similar to that of the left NAcc volume, thereby providing the first evidence linking structural brain development to reward sensitivity in adolescence (Urošević et al., 2012).

The prefrontal cortex is a large, functionally and anatomically heterogeneous region. For this reason, it is difficult to compare the developmental trajectories of specific prefrontal regions of interest across studies, unless other studies have used the same parcellation method. It is unclear which specific prefrontal cortical regions are implicated in the dual systems model, and a variety of studies have found different prefrontal cortical regions involved in risky decision making, reward processing and emotion processing tasks, with inconsistent developmental patterns (Table 4.1).

### 4.1.3 Non-linear behavioural changes between childhood and adulthood

One reason the dual systems model was initially proposed was to account for heightened risk taking in adolescence relative to childhood and adulthood (Steinberg et al., 2008). Recent reviews suggest that non-linear patterns in risky decision making predominantly apply to tasks in which decisions are made in an emotional or social context (e.g., Blakemore & Robbins, 2012). This is consistent with the idea that the heightened risk taking seen during adolescence is likely due to changes in socioemotional processing, rather than resulting from deficiencies in analytical processing or probability judgment (Crone & Dahl, 2012; Reyna & Farley, 2006). The dual systems model predicts a relationship between risk-taking and sensation-seeking behaviours and the developmental mismatch in brain maturation because these behaviours are thought to be influenced by heightened subcortical signaling in adolescence (Casey et al., 2008; Steinberg et al., 2008).

However, impulsivity is associated with the protracted development of the prefrontal cortex but not with subcortical development (Casey, Galvan, & Hare, 2005), and therefore impulsive behaviours are not predicted to be related to the developmental mismatch (Casey et al., 2008). The first aim of this study was to investigate the developmental mismatch hypothesis in a longitudinal sample of MRI scans. The second aim was to assess whether the presence of earlier maturing subcortical regions relative to the prefrontal cortex related to adolescent behaviour, by comparing self-reported levels of adolescent risk-taking, sensation-seeking, and impulsive behaviours – retrospectively assessed by the participants – with each individual's structural brain development pattern.

## 4.2 Methods

### 4.2.1 Participants

The sample consisted of 33 individuals (ages 7–30 years; 10 females), each of whom had undergone at least three structural MRI sessions (152 scans total). These participants were selected from the NIMH Child Psychiatry Branch study of neurotypical brain development for having fulfilled the criteria of having at least three high quality scans across late childhood and adolescence. In the majority of cases (n=32), the sessions spanned three developmental periods: late childhood (7–11 years), adolescence (12–17 years) and early adulthood (18–29 years), with one participant's last session occurring when they were 17 years old. Most participants (31/33) were rated as having completed puberty (Tanner stage 5; Taylor et al., 2001) by their last session, and the two participants without pubertal ratings for their last session were 21 years old. Two individuals were monozygotic twins, and two pairs of individuals were siblings. The IQs of participants in the sample ranged from 99–139 (mean IQ 118±11). There were no

significant differences between females and males in IQ, socioeconomic status (SES), handedness, or number of scans (see Table 4.2). The absence of neurological or psychiatric illness was established through completion of a screening questionnaire (Childhood Behaviour Checklist; Achenbach & Edelbrock, 1991) at each time point. Participants were recruited from the community through local advertisement and were paid for their participation in the study. The institutional review board of the National Institutes of Health approved the research protocol employed in this study and written informed consent and assent to participate in the study were obtained from parents/adult participants and children respectively.

| Participant | Gender | Scans, n | Age range, years |
|---|---|---|---|
| 1 | Male | 5 | 7–21 |
| 2 | Male | 4 | 9–20 |
| 3 | Female | 5 | 11–24 |
| 4 | Female | 6 | 10–28 |
| 5 | Male | 5 | 8–22 |
| 6 | Male | 6 | 7–25 |
| 7 | Female | 5 | 8–20 |
| 8 | Male | 4 | 12–30 |
| 9 | Male | 4 | 10–21 |
| 10 | Female | 6 | 9–26 |
| 11 | Male | 4 | 9–23 |
| 12 | Male | 5 | 10–22 |
| 13 | Male | 4 | 9–19 |
| 14 | Male | 5 | 10–22 |
| 15 | Male | 5 | 9–22 |
| 16 | Male | 4 | 12–22 |
| 17 | Male | 6 | 8–21 |
| 18 | Male | 3 | 12–26 |
| 19 | Male | 4 | 12–23 |
| 20 | Female | 5 | 9–27 |
| 21 | Male | 3 | 12–22 |
| 22 | Female | 5 | 8–20 |
| 23 | Male | 5 | 10–27 |
| 24 | Male | 6 | 11–28 |
| 25 | Female | 5 | 8–23 |
| 26 | Male | 5 | 12–24 |
| 27 | Female | 3 | 11–19 |
| 28 | Male | 5 | 8–21 |
| 29 | Male | 4 | 8–17 |
| 30 | Female | 4 | 10–30 |
| 31 | Female | 4 | 11–18 |
| 32 | Male | 5 | 9–22 |
| 33 | Male | 3 | 8–21 |
| Total | 23 M, 10 F | 152 | 7.0–29.9 |

**Table 4.2. Participant demographics.** Participant numbers (1–33) correspond to graph numbers in Figure 4.4 and participant numbers in table 4.3. The number of scans ranges from 3 to 6 for each participant, with a total of 152 scans. The age at which each individual had their first and last scan varied between individuals, with the overall sample ranging between 7 and 30 years. The sample consisted of 10 females and 23 males, and IQs ranged from 99 to 139. There were no significant differences in IQ, handedness, socioeconomic status, ethnicity, or number of scans between female and male participants.

### 4.2.2 Image acquisition

All MRI scans were T-1 weighted images with contiguous 1.5 mm axial slices and 2.0 mm coronal slices, obtained on the same 1.5-T General Electric Signa scanner (Milwaukee, WI) using a 3D spoiled gradient recalled echo sequence with the following parameters: echo time 5 ms; repetition time 24 ms; flip angle 45° (degree); acquisition matrix 256 × 192; number of excitations 1; and field of view 24 cm. A clinical neuroradiologist evaluated all scans for gross abnormalities.

### 4.2.3 Image processing

To extract reliable volume estimates, images were automatically processed using the FreeSurfer 5.3 longitudinal stream (Reuter et al., 2012). This process includes the creation of an unbiased within-subject template space and image using robust, inverse consistent registration (Reuter et al., 2010). Several processing steps, such as skull stripping, Talairach transforms, atlas registration as well as spherical surface maps and parcellations are then initialised with common information from the within-subject template, significantly increasing reliability and statistical power (Reuter et al., 2012). Cortical grey matter volume ($mm^3$) was measured using the surface-based reconstructed image, and subcortical volumes ($mm^3$) were measured using the volumetric segmentation procedure. This study focused on structural volume because this measure is available for both cortical and subcortical regions. These procedures are detailed in great length in prior

publications and on the FreeSurfer website (surfer.nmr.mgh.harvard.edu; Dale, Fischl, & Sereno, 1999; Fischl et al., 2002; Fischl & Dale, 2000). All images were visually inspected post-processing for accuracy.

### 4.2.4 Regions of interest

Grey matter volume was derived for the amygdala, NAcc, and PFC. The amygdala and NAcc were defined for each individual using FreeSurfer's volumetric segmentation procedure. The PFC was defined using the Desikan-Killiany-Tourville cortical parcellation atlas by combining the following subdivisions: rostral middle frontal, caudal middle frontal, caudal anterior cingulate, and superior frontal (Klein & Tourville, 2012). As some theoretical and empirical papers that discuss the developmental mismatch hypothesise specific roles of the ventromedial PFC (vmPFC) and orbitofrontal cortex (OFC), these regions were analysed separately in a post hoc analysis. These regions were defined using the Desikan-Killiany-Tourville cortical parcellation atlas, with the vmPFC defined as the rostral anterior cingulate subdivision, and the OFC defined by combining the lateral orbitofrontal and medial orbitofrontal subdivisions (Klein & Tourville, 2012). For the purposes of this study, both hemispheric volumes were combined to produce one value for each region of interest (ROI).

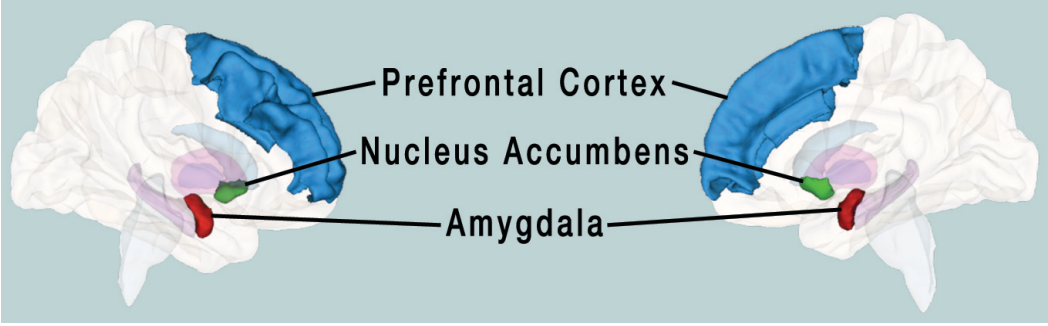


**Figure 4.2. Regions of Interest.** Regions of interest include the amygdala (red), the nucleus accumbens (green) and the prefrontal cortex (blue).

### 4.2.5 Retrospective questionnaire measures

The neuroimaging dataset used in the present report has been acquired over a 20-year period. As no behavioural markers of risk taking were collected from participants concomitantly with the MRI data, this information was collected retrospectively via written questionnaire. Participants were mailed this two-part questionnaire in 2013 to self-assess retrospectively their behaviours during adolescence. The first part of the questionnaire included three questions relating to the individual's general recall of their own teenage behaviour: i) How old were you when you engaged in the most risky behaviour? ii) Compared to your peers, how much risky behaviour did you engage in as a teenager? iii) Please describe the types of risky behaviours you engaged in as a teenager. Risky behaviour was defined in the questionnaire as 'behaviour that is unsafe or might result in negative consequences'. The second part of the questionnaire included adaptations of the following measures: Sensation-seeking Scale (SSS) (Zuckerman, Kolin, Price, & Zoob, 1964), Cognitive Appraisal of Risky Events (CARE) Questionnaire (Fromme, Katz, & Rivet, 1997), Youth Risk Behavior Surveillance (CDC et al., 2013), Barratt Impulsiveness Scale (BIS) (Patton, Stanford, & Barratt, 1995), and Behavioral Inhibition System/Behavioral Approach System Scales (Carver & White, 1994) (see Appendix 4.1 for full questionnaire). Participants were 23–33 years old when they filled out the questionnaire. The present analysis examined risk-taking and sensation-seeking behaviours, which are hypothesised to relate to the developmental mismatch. Self-reported impulsive behaviour was also assessed, although it is not hypothesised to relate to the developmental mismatch.

### 4.2.6 Scoring procedures for retrospective self-reported questionnaire data

For the qualitative question 'please describe the types of risky behaviours you engaged in as a teenager', results were independently scored as low, medium, or high risk taking by two raters who were blinded to the results of the imaging data. Individuals were considered to be high risk takers if they reported at least two behaviours that were considered high risk, including illicit drug use, risky sexual behaviour (unprotected sex, multiple partners), drunk driving and stealing. Medium risk takers reported none or one of the high-risk behaviours as well as multiple less risky activities including graffiti, trespassing and skipping school. Low risk takers reported a maximum of one of the less risky activities, and other low risk activities including scuba diving and toilet papering houses.

Sensation seeking, derived from the SSS, was measured on a scale of 0-6 where six represents high sensation seeking. Participants were asked to read the following six statements and indicate if the statement was true or false for the participant when she or he was a teenager: i) I liked to have new and exciting experiences and sensations even if they were a little frightening; ii) I liked doing things just for the thrill; iii) I liked to do things that were a little frightening; iv) I would try anything once; v) I did 'crazy' things just for fun; and vi) I liked wild and uninhibited parties. Each "true" statement was counted, so that participants could have scores between 0-6.

The BIS was used to derive an impulsivity score between 1 and 4, based on the average rating across the 28-item questionnaire, where 4 represents high impulsivity. Participants were asked to rate 28 questions referring to what the participant was like as a teenager on a scale of 1 (rarely/never), 2 (occasionally), 3

(often), and 4 (usually/always). Of the original 30 questions included in the BIS, two items were removed: “I changed jobs” and “I changed residences” because these questions might not be suitable for some adolescents. Multiple items were adapted to be more appropriate for the period of adolescence.

Risk taking was assessed using 5 sub-scales from the CARE questionnaire depicting sexual risk taking, illicit drug use, alcohol use, aggressive or illegal behaviour and academic risk taking. Each of these is measured using an averaged 7-point scale, where 7 represents engaging in risky behaviours very often, and 1 represents never engaging in risky behaviours. Participants were asked to rate themselves on a scale of 1 (never) to 7 (very often) how often they engaged in 30 separate activities as a teenager. The original CARE questionnaire was adapted by asking participants to rate how often they engaged in these behaviours, rather than asking participants to rate how likely they were to have a positive or negative outcome after engaging in the behaviour. In addition, the behaviour “involvement in sexual activities without my consent” was removed as it was inappropriate for the given study. This item was replaced a more relevant risk behaviour: “carried a weapon." The 30 questions were grouped into 6 subscales: risky sexual activity (5 questions), illicit drug use (3 questions), heavy drinking (3 questions), aggressive or illegal behaviour (10 questions), academic/work risk taking (5 questions), and high-risk sports (4 questions). For the purposes of this study, the subcategory of sports risk taking was not included. One question from the sexual risk-taking subscale was removed: “leaving a social event with someone I have just met” because of its ambiguity and because another question in the subscale was quite similar "had sex with someone I had just met or didn’t know well."

### 4.2.7 Group-level statistical analysis

Mixed-effects modelling was used (R version 3.1-102; nlme package) to analyse the MRI data, thereby allowing an estimation of the fixed effects of measured variables on volume change, while incorporating the longitudinal nature of the data by including within-person variation as nested random effects. The following models were tested for each region of interest:

Linear model: Volume = Intercept + $\alpha$(age)

Quadratic model: Volume = Intercept + $\alpha$(age) + $\beta$(age$^2$)

Cubic model: Volume = Intercept + $\alpha$(age) + $\beta$(age$^2$) + $\gamma$(age$^3$)

Where $\alpha$, $\beta$, and $\gamma$ represent the constant terms defining the effects of each fixed term. Models where the marginal p-value of the highest order variable was significant ($p < 0.05$) were then compared to determine which was the best fit, as determined by Akaike Information Criterion (AIC). All p-values reported in the main text were obtained by likelihood ratio tests comparing the best fitting model against a baseline model that includes only the random effects and not the fixed effects of interest.

### 4.2.8 Individual-level statistical analysis

To compare the developmental changes in the ROIs for each participant, volume measurements at each time point were converted into a percentage of the final time point volume. This made it possible to graph the three ROIs together on one graph for each participant. Under the assumption that relative stability of volume represents structural maturity, two individuals blindly rated whether they detected a mismatch in maturity between each of the regions, which were obscured by

randomising the colors assigned to each region. When these two individuals differed in their ratings, a third blind rater was used to determine the rating. Previous studies have shown a deceleration in volume change across multiple brain structures (including amygdala, caudate, and PFC) between adolescence and adulthood, suggesting that relative stability of volume is an indicator of structural maturity (Pfefferbaum et al., 2013).

## 4.3 Results

### 4.3.1 Group-level brain developmental trajectories

The best fitting model for the amygdala was a quadratic age trajectory (LR = 78.72, $p < 0.0001$), displaying a 7% increase in volume from late childhood until late adolescence, with a deceleration in growth into the early twenties. The best fitting model for the NAcc was a linear age trajectory (LR = 20.83, $p < 0.0001$) displaying a consistent decrease in volume (7% overall) between late childhood and the early twenties. The best fitting model for the PFC was a cubic age trajectory (LR = 238.33, $p < 0.0001$), displaying relative stability in grey matter volume in late childhood, with a 14% decrease in volume beginning in early adolescence, continuing at a similar rate across adolescence and into the early twenties. These support the idea that the amygdala matures during adolescence, whereas the NAcc and PFC are still changing structurally, albeit at different rates and following different patterns, into the twenties. The best fitting model for the vmPFC was a linear age trajectory (LR = 125.08, $p < 0.0001$), displaying a 17% decrease in volume between late childhood and the early twenties. The best fitting model for the OFC was a cubic age trajectory (LR = 148.12, $p < 0.0001$), displaying a 15% decrease in volume between late childhood and the early

twenties. All models, as well as individual volumes, are displayed for each *a priori* ROI in Figure 4.3.

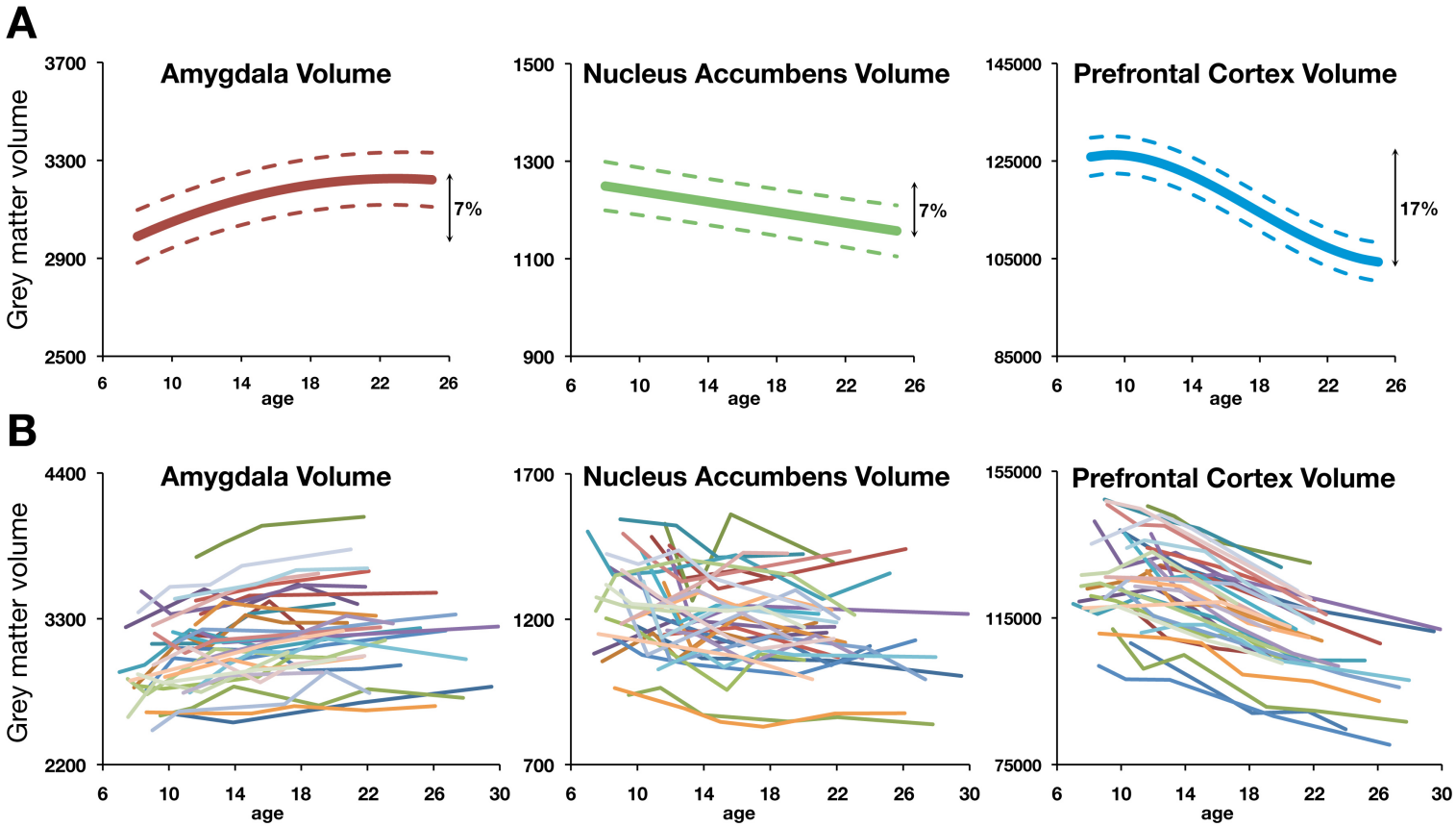


**Figure 4.3. Best fitting group models across all participants and individual trajectories for each ROI.** A) The best fitting model was a quadratic age trajectory for the amygdala (LR = 78.72, $p < 0.0001$), a linear age trajectory for the NAcc (LR = 20.83, $p < 0.0001$) and a cubic age trajectory for the PFC (LR = 238.33, $p < 0.0001$); 95% confidence intervals are displayed as dashed lines. B) The raw values for each individual's developmental trajectories are plotted together on a separate graph for each ROI. Each individual is represented by a color line for visualisation purposes, although we cannot be sure if linear development occurred between each time point. In both panels, age in years is represented on the x-axis, and grey matter volume is represented on the y-axis.

### 4.3.2 Individual-level brain developmental trajectories

Inter-rater reliability between the primary two raters for the MRI data was high (Kappa = 0.795; $p < 0.001$). This temporal mismatch in structural development was observable to a variable extent between individuals. Of the 33 participants, 17 displayed earlier maturation of NAcc compared to the PFC, and 27 displayed faster maturation of the amygdala compared to the PFC. When combining these results to compare all three ROIs, 15 participants (46%) displayed a developmental mismatch in structural maturity between both the amygdala and NAcc compared to the PFC, 12 participants (36%) were labeled as displaying a mismatch between the amygdala only compared to the PFC, two participants (6%) were labeled as displaying a mismatch between the NAcc only compared to the PFC, and four participants (12%) were labeled as displaying no evidence of a mismatch between either the amygdala or NAcc compared to the PFC. The developmental patterns for the three primary ROIs are displayed for each individual in Figure 4.4.

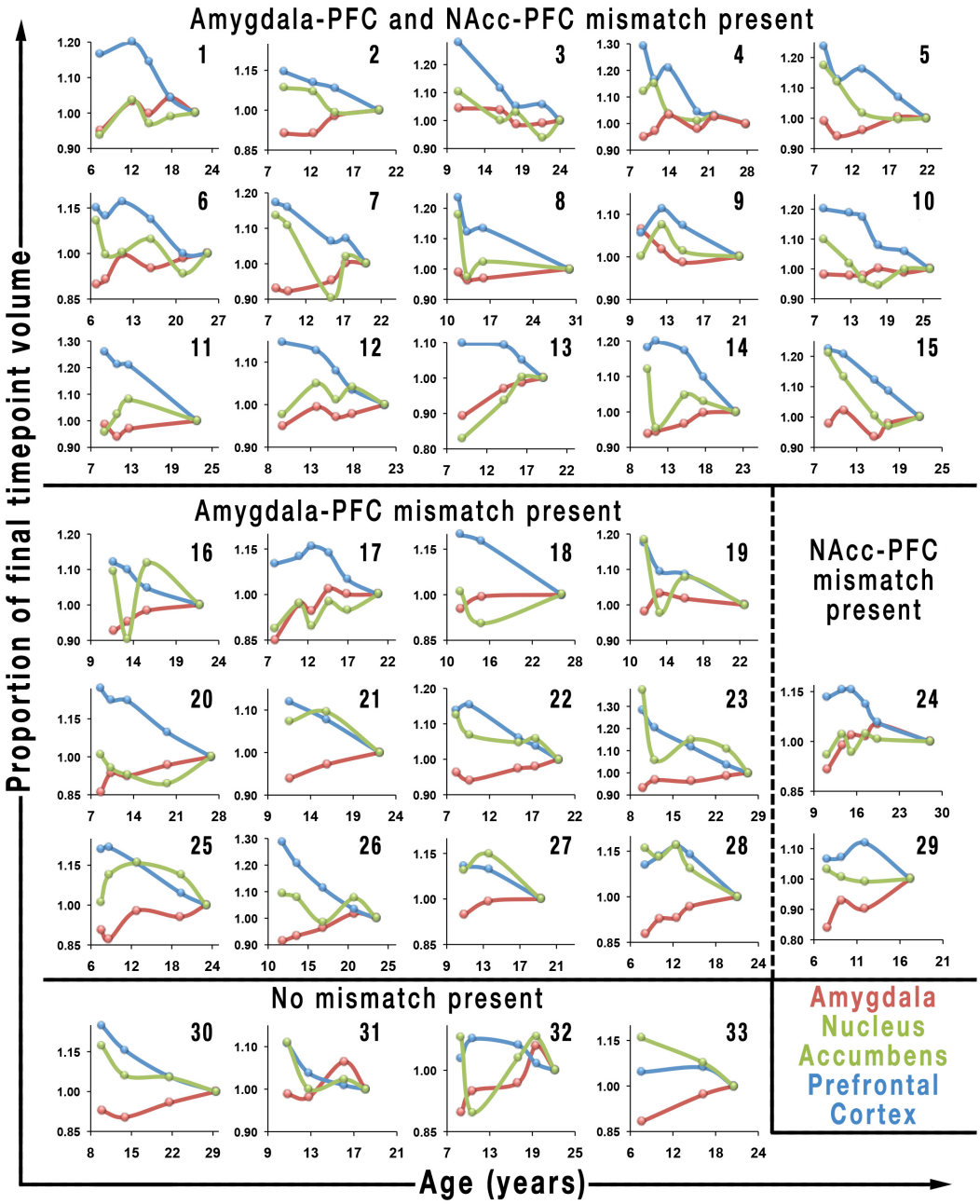


**Figure 4.4. Maturational graphs for each participant**. Each individual's brain developmental patterns for the amygdala (red), nucleus accumbens (green) and prefrontal cortex (blue) are plotted together, with graph numbers corresponding to participant numbers in Tables 4.2 and 4.3. Measurements of volume were converted at each time point into a percentage of the final time point volume. Lines connect the values between time points for each ROI, although it is uncertain as to whether linear development occurred between each time point. Age in years is represented on the x-axis, and proportion of final time point volume is represented on the y-axis. For visualisation purposes, individuals are grouped together based on their pattern of structural brain development. Overall, 15 participants displayed a developmental mismatch in structural maturity between both the NAcc and amygdala compared to the PFC, 12 participants were labeled as displaying a mismatch between the amygdala only compared to the PFC, 2 participants were labeled as displaying a mismatch between the NAcc only compared to the PFC, and 4 participants were labeled as displaying no evidence of a mismatch between either the NAcc or amygdala compared to the PFC.

### 4.3.3 Self-reported risk-taking and sensation-seeking behaviours during adolescence

Twenty-four of the 33 participants (73%) completed the self-report questionnaires. Of these, nine were classified as high risk takers, seven as medium risk takers and eight as low risk takers based on their qualitative answers (see Table 4.3). Two individuals did not list any risk-taking behaviours in the qualitative portion of the questionnaire, and therefore were classified based on their responses to other portions of the questionnaire. These two individuals (participants 3 and 11) were classified as high risk takers. Participants who were categorised as high risk takers based on the qualitative data reported higher levels of risky sexual activity, illicit drug use and alcohol use than participants categorised as medium or low risk takers (one-tailed T-test: sexual activity $p = 0.018$; illicit drug use $p = 0.016$; alcohol use $p = 0.033$). There was no difference between high and medium/low risk-taking groups for aggressive/illegal behaviour ($p = 0.293$) and no clear difference between groups in academic/work risky behaviour ($p = 0.054$). The age of peak risk taking varied from 13 years to 18 years, with three participants reporting that they did not take risks as a teenager. The participants varied in how risky they considered themselves to be in relation to their peers as teenagers: eight considered themselves to be more or much more risky, twelve considered themselves to be less or much less risky, and the remaining four considered themselves to be similar to their peers. There was a large range in participant scores for each of the sub-scales of the CARE questionnaire: risky sexual activity 1.0-6.5; illicit drug use 1.0-6.3; alcohol use 1.0-7.0; aggressive/illegal behaviour 1.0-4.3; academic/work 1.2-6.4. Participants reported a range of sensation-seeking behaviour (median 3.0, range 0-6) and impulsivity (median 2.0, range 1.4-3.4) in adolescence. Participants categorised as

high risk takers reported higher sensation seeking than participants categorised as medium or low risk taking (one-tailed T-test; $p = 0.009$). There was no clear difference between groups in reported adolescent impulsivity (one-tailed T-test; $p = 0.053$).

### 4.3.4 Relationship between brain development patterns and self-reported behaviours

There was no clear pattern of association between the qualitative risk-taking categories and the presence or absence of a mismatch (Table 4.3). Of the nine individuals reporting high levels of retrospective risk-taking activity, three had no developmental mismatch between either the amygdala or the NAcc and the PFC, one showed a mismatch between the NAcc and the PFC, and five showed a mismatch between both the amygdala-PFC and the NAcc-PFC. Within each of the medium and low risk-taking groups, there were participants who showed an amygdala-PFC mismatch, and participants who showed a mismatch between both the amygdala and the NAcc and the PFC. One low risk-taking participant showed no evidence of a developmental mismatch.

| Participant Number | Evidence of structural mismatch | Age at peak risk-taking | Risk taking compared to peers | Qualitiative risk-taking | CARE questionnaire scores | | | | | Sensation-seeking | Impusivity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Sex | Drugs | Alcohol | Aggressive/ Illegal | Academic/ Work | | |
| | | | | | (1-7) | (1-7) | (1-7) | (1-7) | (1-7) | (0-6) | (1-4) |
| **1** | Both | 18 | Less | High | 2.3 | 1.3 | 3.7 | 1.7 | 3.6 | 5.0 | 1.8 |
| 2 | Both | 17 | More | High | 6.5 | 2.0 | 7.0 | 1.6 | 3.0 | 2.0 | 2.9 |
| 3 | Both | 17 | Equivalent | High | 2.5 | 2.0 | 4.0 | 1.7 | 5.4 | 6.0 | 2.8 |
| 5 | Both | 13 | Less | Low | 1.0 | 1.0 | 1.0 | 1.0 | 1.4 | 2.0 | 1.4 |
| 6 | Both | didn't take risks | Much less | Low | 1.0 | 1.0 | 1.0 | 1.4 | 4.6 | 2.0 | 1.9 |
| 7 | Both | 17 | Much less | Medium | 1.0 | 1.0 | 6.3 | 2.1 | 6.4 | 0.0 | 2.9 |
| 8 | Both | 16 | Equivalent | Medium | 1.0 | 3.3 | 5.0 | 1.7 | 4.8 | 3.0 | 2.4 |
| 9 | Both | didn't take risks | Much less | Low | 1.0 | 1.0 | 1.0 | 1.4 | 1.8 | 2.0 | 1.6 |
| 11 | Both | 16 | Much more | High | 3.5 | 3.7 | 4.0 | 3.2 | 6.2 | 6.0 | 2.9 |
| 12 | Both | 15 | More | High | 5.3 | 4.7 | 6.0 | 3.5 | 3.0 | 6.0 | 2.3 |
| 15 | Both | didn't take risks | Less | Low | 1.0 | 1.0 | 1.0 | 2.0 | 1.2 | 2.0 | 1.5 |
| 16 | Amygdala-PFC | 18 | Much less | Low | 1.0 | 1.0 | 2.7 | 1.0 | 2.2 | 2.0 | 1.6 |
| 17 | Amygdala-PFC | 17 | Less | Medium | 1.0 | 1.0 | 1.0 | 1.9 | 1.8 | 3.6 | 1.9 |
| 18 | Amygdala-PFC | 18 | Equivalent | Medium | 2.5 | 2.0 | 4.0 | 2.4 | 3.0 | 3.0 | 2.3 |
| 22 | Amygdala-PFC | 17 | Much less | Low | 3.3 | 1.0 | 1.0 | 1.4 | 2.8 | 1.0 | 2.1 |
| 23 | Amygdala-PFC | 18 | Much more | Medium | 3.5 | 6.0 | 6.7 | 2.5 | 3.2 | 6.0 | 1.9 |
| 24 | Nacc-PFC | 18 | More | High | 4.8 | 6.3 | 5.7 | 2.4 | 3.4 | 6.0 | 1.9 |
| 25 | Amygdala-PFC | 15 | Much more | Medium | 6.0 | 1.3 | 3.3 | 4.3 | 6.0 | 4.0 | 3.4 |
| 27 | Amygdala-PFC | 17 | Much less | Low | 1.0 | 1.0 | 1.3 | 1.4 | 2.8 | 2.0 | 1.7 |
| 28 | Amygdala-PFC | 18 | Much less | Medium | 1.0 | 1.0 | 2.3 | 1.6 | 2.6 | 4.0 | 2.3 |
| 30 | No mismatch | 16 | More | High | 1.0 | 2.3 | 1.7 | 1.0 | 4.2 | 1.0 | 2.7 |
| 31 | No mismatch | 13 | Equivalent | High | 1.0 | 1.7 | 1.0 | 1.6 | 3.2 | 3.0 | 1.8 |
| 32 | No mismatch | 18 | Less | Low | 1.0 | 1.0 | 2.7 | 2.0 | 3.0 | 0.0 | 1.8 |
| 33 | No mismatch | 17-18 | More | High | 4.8 | 5.0 | 7.0 | 1.9 | 5.2 | 6.0 | 2.5 |

**Table 4.3.** Results from the 24 participants that completed the retrospective questionnaire are summarised in this table. Participant numbers correspond to graph numbers in Figure 4.4 and participant numbers in Table 4.2. Evidence for a structural mismatch is listed alongside results from the questionnaire. Self-reported age at peak risk taking during the teen years is listed, as well as how participants felt about their risk-taking behaviour in comparison to their peers. Participants were categorised as high, medium or low risk takers based on their responses to the qualitative portion of the questionnaire. Risk taking was assessed using 5 subscales from the CARE questionnaire depicting sexual risk taking, illicit drug use, alcohol use, aggressive or illegal behaviour, and academic risk taking. Each of these is measured using an averaged 7-point scale, where 7 represents engaging in risky behaviours very often, and 1 represents never engaging in risky behaviours. Sensation seeking, derived from the SSS, was measured on a scale of 0 – 6 where 6 represents high sensation seeking. The BIS was used to derive an impulsivity score between 1 and 4, based on the average rating

## 4.4 Discussion

This study investigated two hypotheses proposed by the dual systems model: that subcortical regions involved in affect and reward (the amygdala and NAcc) mature (as assessed by structural volume stability) before the prefrontal cortex in neurotypically developing individuals; and that this developmental mismatch in maturity relates to retrospective self-reported risk-taking and sensation-seeking behaviours during adolescence. This study examined both group- and individual-level patterns of structural brain development in a sample of 33 individuals who had undergone at least three structural MRI scans between late childhood and early adulthood, and related these patterns of brain development to retrospectively assessed self-reported measures of risk-taking, sensation-seeking, and impulsive behaviour during adolescence in a subgroup of 24 individuals.

### 4.4.1 Evidence for a structural developmental mismatch

The results of this study show subcortical volumes maturing earlier than the PFC at both group- and individual-levels, with the developmental mismatch more prevalent between the amygdala and PFC than between the NAcc and PFC. Within the whole group, the amygdala increased in volume from late childhood until late adolescence, with a decelerating rate of growth after age 16 years. In contrast, the PFC showed little change in grey matter volume in childhood, and began decreasing in volume around early adolescence, and this decline persisted into young adulthood. This result is in keeping with previous findings that have shown relatively earlier maturation of the amygdala (as judged by stable structural volume on MRI) compared to the prefrontal cortex at a group level (Tamnes, Walhovd, Dale, et al., 2013). For the NAcc, the best fitting group model displayed a linear decrease in volume throughout the studied age range (between ages 8 and

25 years). This result is similar to that found in previous longitudinal studies of NAcc structural development (e.g., Goddings et al., 2013; Tamnes, Walhovd, Dale, et al., 2013), which also reported linear decreases in adolescence, although there have been contrasting results (see Dennison et al., 2013; Urošević et al., 2012). Taken together, the current report and previous studies suggest that, at a group level, the NAcc decreases in volume between adolescence and adulthood, whereas the amygdala likely increases in late childhood and early adolescence before stabilising in volume by mid to late adolescence, with significant inter-individual variability in the development of both regions.

In the present study, the prefrontal cortical region was defined as the combined volumes of the dorsolateral prefrontal cortex and dorsal anterior cingulate cortex. This region displayed the highest grey matter volume in late childhood and early adolescence, and showed consistent decreases in grey matter volume (between 1.2%-1.7% per year) across the teen years before decelerating in the early twenties. This finding is consistent with findings from other longitudinal samples, which have shown decreasing grey matter volume in the PFC between late childhood and early adulthood (Pfefferbaum et al., 2013; Tamnes, Walhovd, Dale, et al., 2013). Comparing all three regions of interest at a group level, these data lend support to a structural mismatch in developmental timing between the amygdala and the PFC, but do not provide evidence of a clear structural mismatch between the NAcc and the PFC during adolescence, since both regions continue to show volume change into early adulthood.

At an individual level, the results show wide variation in the presence or absence of a developmental mismatch between structures. Nearly half of the participants

in the study were judged to exhibit a mismatch between both subcortical structures and the PFC, whilst four participants showed no evidence of a difference in developmental timing between structures. Again, the relationship between the developmental timings of the amygdala and PFC was more consistent, with 27 out of 33 participants (82%) showing a mismatch, further supporting the idea that the amygdala matures before the PFC, with the amygdala stabilising in volume in mid-to-late adolescence, and the PFC continuing to change in volume until at least the mid-twenties. The results are more ambiguous regarding the NAcc. Half of the sample was judged to show an earlier-developing NAcc compared to the PFC, supporting the developmental mismatch hypothesis for structural maturation, but the remainder of the sample did not. This wide variation at an individual level, disguised by the group level analysis, highlights differential patterns of brain growth, and emphasises the need for further investigation and quantification of the extent and impact of individual differences in brain development. Recent reviews of the dual systems hypothesis have postulated that the relationship between the differing brain networks involved in reward and cognitive control are more nuanced and complex than is allowed by this model (Crone & Dahl, 2012; Pfeifer & Allen, 2012). Further investigation of these individual differences in brain development may help unravel some of these additional complexities.

It is not possible to identify the specific neuroanatomical and physiological events contributing to the volume changes observed across development using currently available MRI techniques (see Chapter 2 for in-depth discussion). Although the cellular mechanisms that underlie the changes in grey matter captured by MRI are still unknown, they are likely to reflect interacting cellular events that differ

between subcortical and cortical structures. Decreases in grey matter volume in the PFC across the second decade occur concomitantly with decreases in dendritic spine density in Brodmann area 9 (Petanjek et al., 2011), decreases in synaptic density in the anterior third of the middle frontal gyrus (Huttenlocher & Dabholkar, 1997), increases in intracortical myelination across the cortex (Yakovlev & Lecours, 1967), and increases in subcortical white matter volume (Aubert-Broche et al., 2013; Lebel & Beaulieu, 2011). Each of these processes is likely to have an impact on measures of prefrontal grey matter volume during the second decade. The increase in amygdala volume observed between late childhood and adolescence could reflect pubertal neurogenesis and gliogenesis in the amygdala, which has recently been found in Syrian hamsters (Mohr & Sisk, 2013). Similar processes might also underlie the decrease in NAcc volume; however, there are few histological studies examining changes in NAcc volume across development (Sturman & Moghaddam, 2011). The physiological mechanisms underlying all these developmental changes are still relatively poorly understood, but the possibility that differential processes are responsible for the development of these different regions may help to explain the variation between individuals in the presence or absence and extent of a developmental mismatch. Thus, in some individuals there may be a long chronological gap separating the processes leading to subcortical and cortical maturation, leading to an extended developmental mismatch in maturation, whilst in other individuals the processes may better align, resulting in a diminished, or completely absent, mismatch.

### 4.4.2 Relating a structural mismatch to brain function and behaviour

The demonstration of a structural mismatch in development between the amygdala-PFC and NAcc-PFC in a proportion of individuals provides some

support for the underlying dual systems hypothesis. However, the link between neuroanatomical maturity and either functional brain changes or behaviour is unclear. The original dual systems hypothesis drew together evidence from a variety of sources including animal behaviour, neurophysiology, functional neuroimaging, and large epidemiology studies to form a population-based theory linking brain maturation and risk-taking behaviour in adolescence (Casey et al., 2008; Steinberg, 2008). There have been a number of cross-sectional functional neuroimaging studies supporting the idea that, during adolescence, there is heightened recruitment of subcortical regions involved in tasks involving risky decision making, reward processing and emotion processing (Table 4.1). One early study noticed that adolescents and adults showed a similar "refined" pattern of BOLD signal in the NAcc while processing reward, whereas adolescents and children showed a diffuse pattern of activity in the OFC (Galvan et al., 2006). Based on the "diffuse to focal" hypothesis of brain maturation (Casey et al., 2005), the authors interpreted these finding as evidence for the earlier NAcc development relative to the OFC. However, the diffuse to focal hypothesis has received less support in subsequent years, as findings have been inconsistent (Poldrack, 2010), and it is unclear how developmental changes in BOLD signal relates to developmental changes in grey matter volume. Patterns of functional connectivity, both intrinsic (resting-state) and task-based, have been used as a measure of functional maturity (Dosenbach et al., 2010; Gee et al., 2013). Between ages of 4 and 22 years, functional connectivity between the medial PFC and amygdala during a fearful face processing task decreases substantially, in parallel with decreased amygdala reactivity to the fearful faces (Gee et al., 2013). However, given the extent of individual variability in both brain structure and

function, longitudinal fMRI studies are needed to describe the maturational trajectories of functional connectivity.

The current study used individual variability in the presence or absence of a structural developmental mismatch to tentatively investigate whether the existence of a developmental mismatch in the brain relates to an individual's level of risk-taking behaviour. This analysis was exploratory, since previous studies have not attempted to relate the relative maturation between different brain regions, either in terms of function or structure, to behaviour within the same individuals. This study was unable to find any correlation between the level of self-reported risk-taking behaviour and the presence or absence of a developmental mismatch between the regions of interest. Three of the participants categorised as high risk takers during adolescence, who reported behaviours including illicit drug use and unsafe sexual behaviour, showed no mismatch (see Table 4.3), and the participants who showed a convincing structural mismatch between regions reported a wide variation in behaviour from very risk-averse to very risk-seeking.

The absence of correlation between structural brain development and risk-taking behaviour in this sample may simply result from the limitations associated with this study, including the small sample size and the retrospective nature of the risk-taking data (discussed further below). Nevertheless, the finding highlights the need for further work to ascertain whether a developmental mismatch in brain development is associated with behaviour within individuals, as opposed to simply at a population level. The absence of correlation in this sample might reflect the mismatch being associated with relatively increased risk taking within

an individual, as opposed to an absolute high level of risk-taking behaviour. Thus, an individual may find themselves being riskier in adolescence than they were during either childhood or adulthood, but still might not engage in 'high risk' activities typically assessed by standard measures.

### 4.4.3 Limitations

This study used longitudinal MRI data collected between 1991 and 2011, as well as retrospectively assessed self-reported questionnaire data. The relatively small sample size of the current study is partly the result of the eligibility criteria: only scans of high quality that were accurately reconstructed using FreeSurfer 5.3's longitudinal pipeline were included in the sample. Despite the best efforts to include only high quality scans, I cannot be certain of the amount of error present in the segmentation of the amygdala and NAcc, or in the reconstruction of the PFC. The NAcc is a small structure, and its developmental trajectory may be disproportionately affected by error, which could account for some of the fluctuations seen in the individual trajectories displayed in Figure 4.3b. In addition, I cannot be sure how each ROI changed between each time point, and the connecting lines used for visualisation purposes in Figure 4.3b and Figure 4.4 should be interpreted with caution. However, it is worth noting that the sample size of the current study is large enough to detect, with 80% statistical power, the magnitude of changes observed in the three brain structures examined (Steen et al., 2007). Steen et al. estimated that a sample size of 5 participants would be required for a longitudinal study to detect a 5% change in the grey matter volume of just the left frontal cortex, and a sample size of 47 is needed to detect this change for the left caudate nucleus. While the nucleus accumbens is slightly smaller than the caudate, as I combined the values for both hemispheres and also

detected a larger change (7%) in this study, it is likely that the present sample was able to obtain the observed effects with 80% statistical power.

The ability to interpret the behavioural results of the present study are impacted by the uncertainty associated with both self-report questionnaires and retrospective assessment (Schwarz et al., 1994). Because of this limitation, I encourage readers to interpret the behavioural results with caution, and suggest that future studies implement concurrent measurement of risk-taking and sensation-seeking behaviours (via self-report or behavioural paradigms) with MRI data collection.

## 4.5 Conclusion

The results of the present study support the idea that the amygdala matures before the PFC, as the amygdala stabilises in volume in mid-to-late adolescence, whereas the PFC continues to change in volume until at least the mid-twenties. The results are more ambiguous regarding the NAcc. This study did not find a relationship between individual patterns of brain development and adolescent risk-taking or sensation-seeking behaviours.

# Chapter 5 Structural development of the social brain across adolescence

## 5.1 Introduction

Mentalising, the ability to infer the intentions, beliefs and desires of others in order to predict their behaviour, is fundamental to human development. In a large number of functional neuroimaging studies using a wide variety of mentalising tasks, the process of mental state attribution has been associated with a network of brain regions that include the medial prefrontal cortex (mPFC), temporoparietal junction (TPJ), posterior superior temporal sulcus (pSTS) and anterior temporal cortex (ATC) (Blakemore, 2012; U. Frith & Frith, 2003). Developmental fMRI studies have shown changes in recruitment within this "social brain network" across adolescence (see Introduction for review). For many years, it was assumed that social cognitive development was mostly complete in childhood (Wimmer & Perner, 1983). However, recent behavioural research demonstrates that online social cognitive skills improve across adolescence (Dumontheil, Apperly, et al., 2010). Several fMRI studies have shown differences in functional recruitment of the social brain network between adolescence and adulthood during social cognitive tasks (Blakemore, 2012). Despite the variety of paradigms used, from irony comprehension (Wang et al., 2006) to thinking about social emotions like guilt (Burnett et al., 2009), many developmental fMRI studies of social cognition to date have reported decreased recruitment of dorsal mPFC in adolescents as compared to adults (see Introduction). In some studies, higher activity in more posterior regions, such as the pSTS/TPJ (Blakemore et al., 2007), and in the ATC (Burnett et al., 2009), was observed in adults as compared to adolescents. These changes in functional recruitment have been hypothesised to reflect changes in

neurocognitive strategy and/or neuroanatomy (Blakemore, 2008). As decreases in functional activity can co-occur with reductions in grey matter volume (Cohen Kadosh, Johnson, Dick, et al., 2012; Lu et al., 2009), it is informative to describe the typical structural developmental trajectories of social brain regions. However, how the different regions of the social brain develop *structurally* in this period of life is not well detailed. This study investigated structural development in regions of the social brain network from ages 7 to 30 years using data from the largest longitudinal pediatric neuroimaging sample (Giedd et al., 1996).

Whereas previous studies have investigated changes in structure across the entire brain, this study's analysis was limited to four *a priori* regions of interest within the social brain network. I used surface-based cortical reconstruction software to distinguish grey matter volume, cortical thickness and surface area trajectories in these regions of interest. As previous studies using both lobar-level and whole brain analytic approaches have shown inverted-U shaped trajectories in grey matter volume and cortical thickness across the frontal, temporal and parietal cortices, I predicted similar trajectories in all regions examined in our analysis. However, changes in surface area across development have been less well characterised, and I predicted that the surface area would show an inverted-U shaped trajectory with an inflection in early/pre-adolescence, similar to what was found by Raznahan et al. (2011) for the entire cortex. Although I did not predict sex differences in these regions based on differential social cognitive development between females and males, based on previous brain imaging studies I predicted that females would show an earlier decrease in grey matter volume and surface area, but not in cortical thickness, than males (Raznahan et al., 2011).

## 5.2 Methods

### 5.2.1 Participants

The sample consisted of 288 unrelated individuals (124 females, 164 males), each of whom had undergone two or more high quality MRI scans ~2 years apart over the age range of 7–30 years. The average age of that participants displayed the earliest signs of pubertal onset (Tanner Stage 2), as measured by a self-report (parents or participants) pubertal developmental scale in a subset of individuals (41 females, 51 males), was 10.01 years (9.94 for females, 10.06 for males). As adolescence is defined as the time period between puberty and relative self-sufficiency, this study defines adolescence as roughly 10–18 years of age. Of the 288 individuals, 126 were members of twin pairs (55 females, 71 males); only one member per twin pair was included in the analysis. There were no significant differences between males and females in socioeconomic status, handedness, ethnicity, IQ, or number of scans (see Table 5.1). The absence of neurological or psychiatric illness was established through a telephone screening interview and completion of a parent-report screening questionnaire (Childhood Behavior Checklist; Achenbach & Edelbrock, 1991). Handedness was established using Physical and Neurological Examination of Soft Signs inventory (PANESS; Denckla, 1984). All participants had a full-scale intelligence quotient (IQ) greater than 80 (IQ was estimated using age-appropriate Wechsler Intelligence Scales). Socioeconomic status (SES) was quantified using Hollingshead scales (Hollingshead, 1975). Sample characteristics are detailed in Table 5.1.

| Characteristic | Group | | | Sex difference |
|---|---|---|---|---|
| | All | Female | Male | |
| Number of individuals | 288 | 124 | 164 | n.s. |
| Singleton | 162 | 69 | 93 | |
| Member of twin pair | 126 | 55 | 71 | |
| Handedness, no. | | | | n.s. |
| Right | 255 | 107 | 148 | |
| Mixed | 21 | 10 | 11 | |
| Left | 11 | 7 | 4 | |
| Race, no. | | | | n.s. |
| Caucasian | 250 | 107 | 143 | |
| African-American | 21 | 10 | 11 | |
| Asian | 2 | 1 | 1 | |
| Hispanic | 8 | 4 | 4 | |
| Other | 7 | 2 | 5 | |
| IQ | | | | n.s. |
| Mean (s.d.) | 114 (12.0) | 113 (12.5) | 115 (11.5) | |
| SES | | | | n.s. |
| Mean (s.d.) | 41 (18.2) | 42 (17.5) | 40 (18.7) | |
| Number of scans, no. | | | | n.s. |
| 2 scans | 138 | 60 | 78 | |
| 3 scans | 73 | 36 | 37 | |
| 4 scans | 40 | 11 | 29 | |
| 5 scans | 23 | 12 | 11 | |
| 6 scans | 11 | 5 | 6 | |
| 7 scans | 3 | 0 | 3 | |
| Total | 857 | 362 | 495 | |
| Age distribution of scans (years) | | | | |
| Mean (s.d.) | 14.9 (4.9) | 14.4 (4.9) | 15.2 (4.8) | |
| Range | 7.0–30.6 | 7.1–29.5 | 7.0–30.6 | |

**Table 5.1. Participant demographics.** There were no significant differences in IQ, handedness, SES, ethnicity or number of scans between female and male participants. n.s., not statistically significant at $p < 0.05$.

Participants were recruited from the community through local advertisement and paid for their participation in the study (Giedd et al., 1996). The institutional review board of the National Institutes of Health approved the research protocol employed in this study and written informed consent and assent to participate in the study were obtained from parents/adult participants and children respectively.

### 5.2.2 Image Acquisition

All MRI scans were T-1 weighted images with contiguous 1.5 mm axial slices and 2.0 mm coronal slices, obtained on the same 1.5-T General Electric Signa scanner (Milwaukee, WI) using a 3D spoiled gradient recalled echo sequence with the following parameters: echo time, 5 ms; repetition time, 24 ms; flip angle 45° (degree); acquisition matrix, 256 × 192; number of excitations, 1; and field of view, 24 cm. A clinical neuroradiologist evaluated all scans for gross abnormalities.

### 5.2.3 Image processing

Cortical reconstruction was performed with the FreeSurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications (Dale et al., 1999; Fischl et al., 1999). The processing stream for structural images includes motion correction (Reuter et al., 2010), removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Ségonne et al., 2004), automated Talairach transformation, intensity normalisation (Sled et al., 1998), tessellation of the grey matter white matter boundary, automated topology correction (Fischl et al., 2001; Ségonne et al., 2007), and surface deformation following intensity gradients to optimally place the grey/white and grey/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale et al., 1999; Dale & Sereno, 1993; Fischl & Dale, 2000). For the purposes of this analysis, two surface area measurements were averaged together to obtain a measurement of the middle grey surface area. I visually inspected each cortical reconstruction, and unsuccessful cortical reconstructions were identified and

excluded from the present analyses. This left a sample of 288 individuals (857 scans) for the analyses of the mBA10, TPJ and pSTS, and a sample of 221 individuals (447 scans) for the analysis of the ATC. Each cortical model was registered to a spherical atlas using individual cortical folding patterns to match cortical geometry across subjects (Dale et al., 1999). Measurements of mean cortical thickness (mm), middle grey surface area ($mm^2$), and grey matter volume ($mm^3$) were extracted for each region of interest.

### 5.2.4 Regions of Interest

Four regions of interest (ROIs) were created for each hemisphere using an averaged template in FreeSurfer. These ROIs, illustrated in Figure 5.1, include medial Brodmann Area 10 (mBA10), temporoparietal junction (TPJ), posterior superior temporal sulcus (pSTS) and anterior temporal cortex (ATC). As the present analysis necessitated well-defined borders for all ROIs, I chose mBA10 as a proxy for dorsal mPFC. The mBA10 itself has been characterised in meta-analyses as a neural correlate of mentalising (Gilbert et al., 2006). Structural measurements for each hemisphere were combined to produce one value for each ROI. Post-hoc analyses for the left and right hemispheres were performed to examine hemispheric differences. Details of how each region was defined are detailed below.

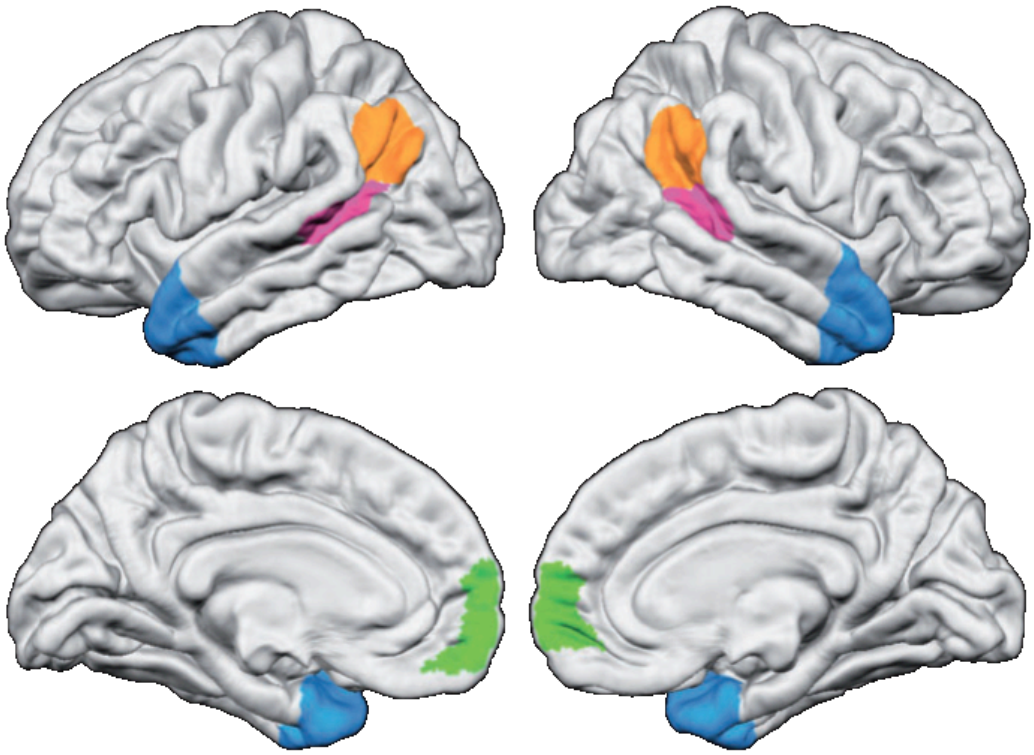

**Figure 5.1. Regions of Interest.** Social brain regions of interest include medial Brodmann Area 10 (mBA10; green), temporoparietal junction (TPJ; orange), posterior superior temporal sulcus (pSTS; pink) and anterior temporal cortex (ATC; blue).

*mBA10*– The medial portion of BA10 was defined using the PALS B12 Brodmann atlas projected onto an averaged FreeSurfer template (Van Essen, 2005). From this atlas, the BA10 label was selected, and any area of this label located outside of the medial cortex was eliminated.

*TPJ*– The TPJ was defined using the border coordinates of a functional subdivision generated in a previous study (Mars et al., 2012). This study defined three consistent functional subregions within a larger TPJ area in the right hemisphere, each with unique functional and structural connectivity profiles. Of the three subregions, I chose to use the posterior TPJ subregion, as it was functionally connected to other areas of the social brain including mBA10 and ATC (Mars et al., 2012).

*pSTS*– The pSTS region was created by extending the Desikan-Killiany Atlas defined bank STS (Desikan et al., 2006; Fischl et al., 2004) to the border of the TPJ.

*ATC*– The ATC was defined by extending the temporal pole, defined as Brodmann Area 38 in the PALS B12 Brodmann atlas, back to include areas of the ATC responding to mentalising tasks in previous fMRI studies (Olson, Plotzker, & Ezzyat, 2007).

### 5.2.5 Statistical Analysis

I used mixed-effects modelling (Pinheiro & Bates, 2000) to estimate the fixed effects of age on each measure, with nested random effects terms modelled for within person dependence of observations. For example, an equation for a model using cubic grey matter volume (GM) growth for *i*th individual's *j*th time point is: $GM_{ij} = \text{Intercept} + d_i + \beta_1(\text{age}) + \beta_2(\text{age}^2) + \beta_3(\text{age}^3) + \varepsilon_{ij}$. Age terms were centered to the mean age (i.e., the mean age, 14.89 years, was subtracted from each age) to reduce the correlation between the age, age-squared, and age-cubed terms. For each measure, an *F* test was first performed to test to see if the model was a significant fit, then Akaike Information Criterion (AIC) was used to determine whether a cubic, quadratic or linear growth model best fit the entire sample.

After determining the best growth model for the entire sample, I conducted likelihood ratio (LR) tests to determine if the growth curves were statistically different between sexes. First, to establish if the brain measurements were significantly different overall between males and females, I conducted a likelihood ratio test to determine whether the best fitted model including age and a

main effect of sex predicted significantly more variance in the measure of interest compared with the model including age terms alone. Second, to establish if the growth curve shape for the measure of interest was significantly different between males and females, I conducted a likelihood ratio test to determine whether the best fitted model including interactions between age terms and sex predicted significantly more variance in the measure of interest compared with a simpler model including only age terms and a main effect of sex.

## 5.3 Results

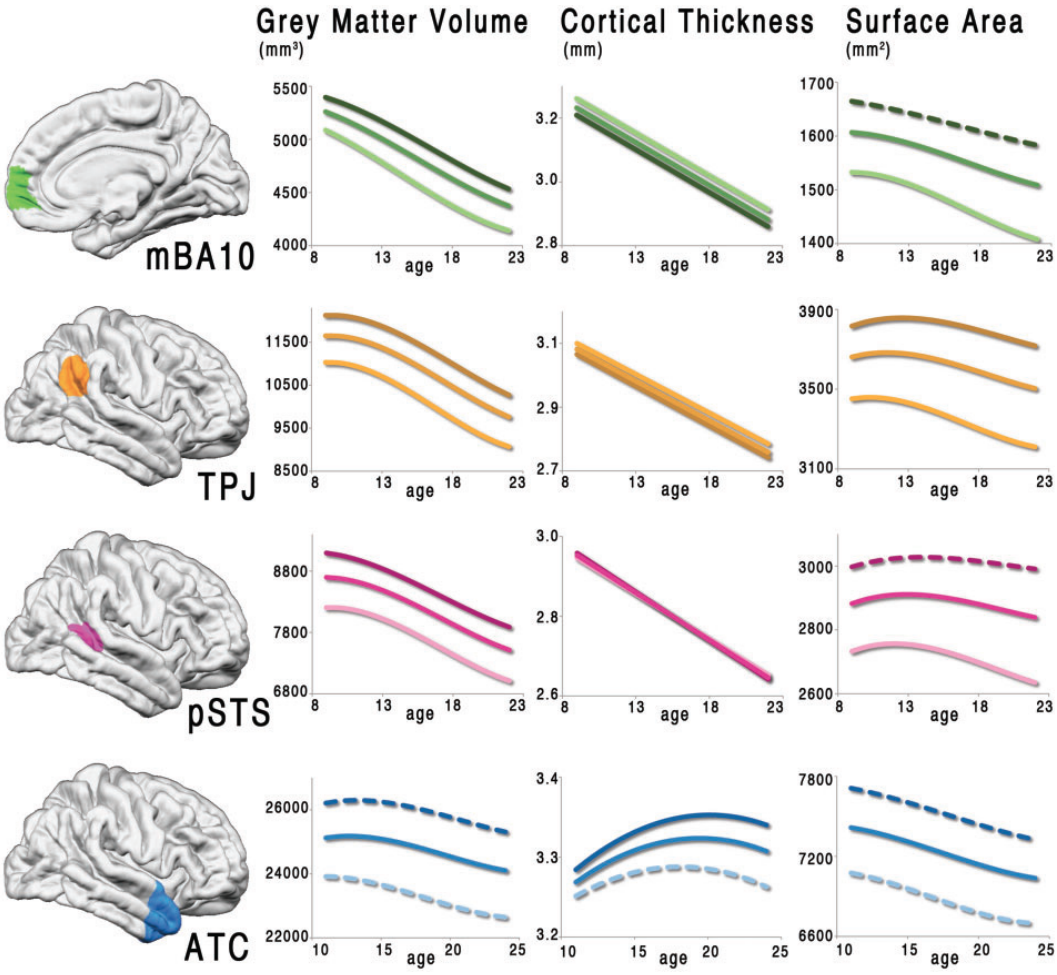


**Figure 5.2. Best fitting models for combined hemispheres.** The best fitting models for all participants are shown for each region of interest (combined hemispheres). Models are fitted to the middle 80% of the sample (ages 9–22 years for mBA10, TPJ and pSTS; ages 11–24 years for ATC). The lighter lines show the fitted models applied to females only, and the darker lines show the fitted models applied to males only. Solid lines indicate the fitted model was significant $p < 0.05$, whereas dashed lines indicate the fitted model was not significant ($p \geq 0.05$).

### 5.3.1 Medial BA10

Grey matter volume for mBA10 followed a cubic trajectory ($F_{(1,566)} = 9.51$, $p < 0.003$), decreasing steadily from age 9 to 22 years. Cortical thickness for mBA10 decreased linearly from childhood into the early twenties ($F_{(1,568)} = 329.34$, $p < 0.001$), whereas the surface area followed a cubic trajectory ($F_{(1,566)} = 5.67$, $p < 0.018$), decreasing from late childhood into the early twenties (Figure 5.2). Grey matter volume for the left mBA10 followed a linear trajectory ($F_{(1,568)} = 219.46$, $p < 0.0001$), and right mBA10 followed a cubic trajectory ($F_{(1,566)} = 12.72$, $p < 0.0005$). Cortical thickness for the left mBA10 followed a quadratic trajectory ($F_{(1,567)} = 7.93$, $p < 0.006$), and right mBA10 followed a cubic trajectory ($F_{(1,566)} = 7.18$, $p < 0.008$). Surface area for the left mBA10 followed a linear trajectory ($F_{(1,568)} = 32.97$, $p < 0.0001$), and right mBA10 followed a linear trajectory ($F_{(1,568)} = 89.11$, $p < 0.0001$) (Figures 5.3 & 5.4).

### 5.3.2 TPJ

Grey matter volume for the TPJ followed a cubic trajectory ($F_{(1,566)} = 44.06$, $p < 0.0001$), decreasing steadily from age 10 to 22 years. Cortical thickness for the TPJ decreased linearly from childhood into the early twenties ($F_{(1,568)} = 475.81$, $p < 0.0001$), whereas the surface area followed a cubic trajectory ($F_{(1,566)} = 14.73$, $p < 0.0002$), decreasing from age 13 into the early twenties. Grey matter volume for the left TPJ followed a cubic trajectory ($F_{(1,566)} = 20.00$, $p < 0.0001$), and right TPJ followed a cubic trajectory ($F_{(1,566)} = 37.46$, $p < 0.0001$). Cortical thickness for the left TPJ followed a linear trajectory ($F_{(1,568)} = 341.44$, $p < 0.0001$), and right TPJ followed a linear trajectory ($F_{(1,568)} = 354.93$, $p < 0.0001$). Surface area for the left

TPJ followed a cubic trajectory ($F_{(1,566)} = 10.73$, $p < 0.002$), and right TPJ followed a cubic trajectory ($F_{(1,566)} = 6.306, p < 0.02$).

### 5.3.3 pSTS

Grey matter volume for the pSTS followed a cubic trajectory ($F_{(1,566)} = 25.90, p < 0.0001$), decreasing steadily from age 9 to 22 years. Cortical thickness for the pSTS decreased linearly from childhood into the early twenties ($F_{(1,568)} = 574.07, p < 0.0001$), whereas the surface area followed a cubic trajectory ($F_{(1,568)} = 6.98, p < 0.009$), decreasing from age 13 into the early twenties. Grey matter volume for the left pSTS followed a cubic trajectory ($F_{(1,568)} = 16.39, p < 0.0002$), and right pSTS followed a cubic trajectory ($F_{(1,566)} = 14.98, p < 0.0002$). Cortical thickness for the left pSTS followed a linear trajectory ($F_{(1,568)} = 444.21$, $p < 0.0001$), and right pSTS followed a linear trajectory ($F_{(1,568)} = 335.75$, $p < 0.0001$). Surface area for the left pSTS followed a linear trajectory ($F_{(1,568)} = 12.17$, $p < 0.0006$), and right pSTS followed a cubic trajectory ($F_{(1,566)} = 4.82, p < 0.03$).

### 5.3.4 ATC

Grey matter volume for the ATC followed a cubic trajectory ($F_{(1,223)} = 7.67$, $p < 0.007$), with the greatest volume observed in late childhood and early adolescence, before decreasing into the mid-twenties. Cortical thickness followed a quadratic trajectory, increasing from childhood throughout the teen years ($F_{(1,224)} = 11.50$, $p < 0.0009$), whereas surface area followed an cubic trajectory ($F_{(1,224)} = 4.52, p < 0.04$), decreasing from late childhood into the mid-twenties. Grey matter volume for the left ATC followed a linear trajectory ($F_{(1,225)} = 13.40, p < 0.0004$), and right ATC followed a cubic trajectory ($F_{(1,223)} = 9.29$, $p < 0.003$). Cortical thickness for the left ATC followed a quadratic trajectory ($F_{(1,224)} = 5.56$, $p <$

0.02), and right ATC followed a linear trajectory ($F_{(1,225)} = 5.78, p < 0.02$). Surface area for the left ATC followed a linear trajectory ($F_{(1,225)} = 31.75, p < 0.0001$), and right ATC followed a cubic trajectory ($F_{(1,223)} = 5.70, p < 0.02$).

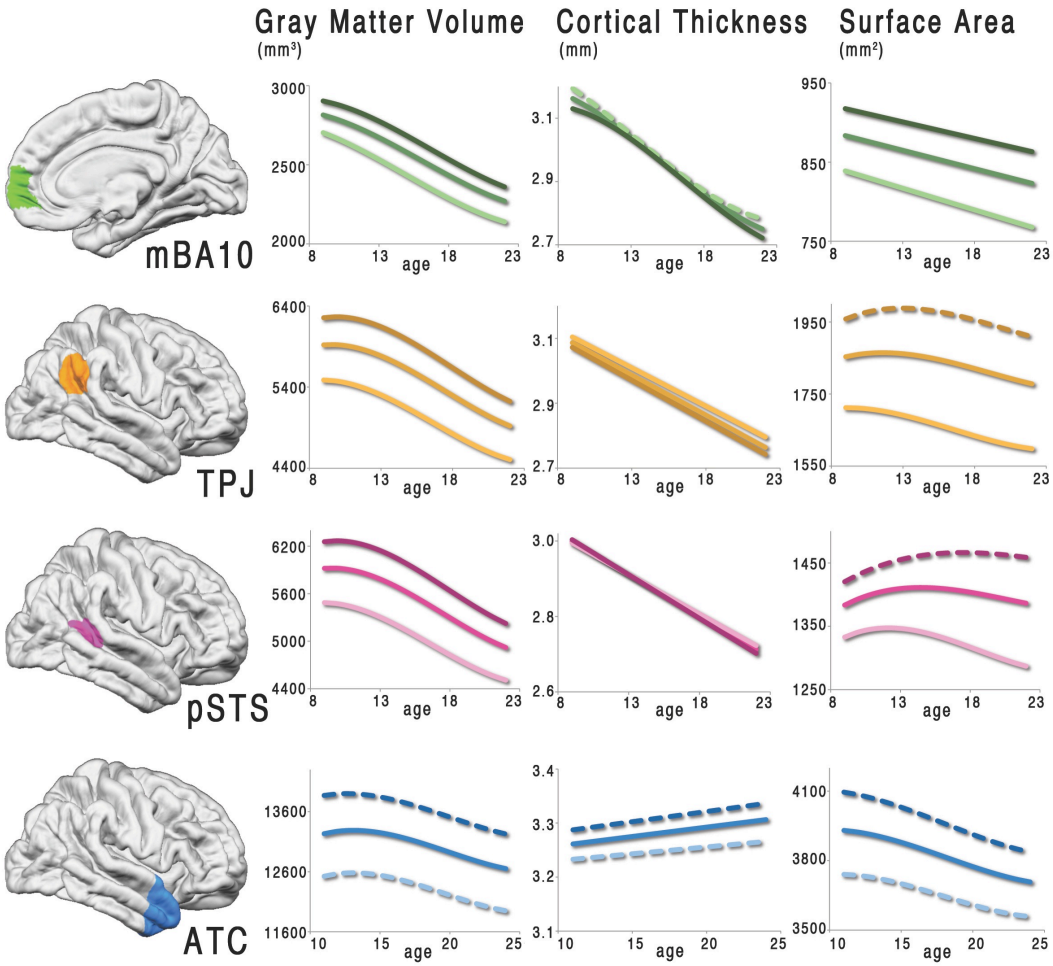


**Figure 5.3. Best fitting models for the right hemisphere only**. The best fitted models for all participants are shown for each region of interest measured on the right hemisphere only. Models are fitted to the middle 80% of the sample (ages 9–22 for mBA10, TPJ and pSTS; ages 11–24 for ATC). The lighter lines show the fitted models applied to females only, and the darker lines show the fitted models applied to males only. Solid lines indicate the fitted model was significant $p < 0.05$, whereas dashed lines indicate the fitted model was not significant ($p \geq 0.05$).

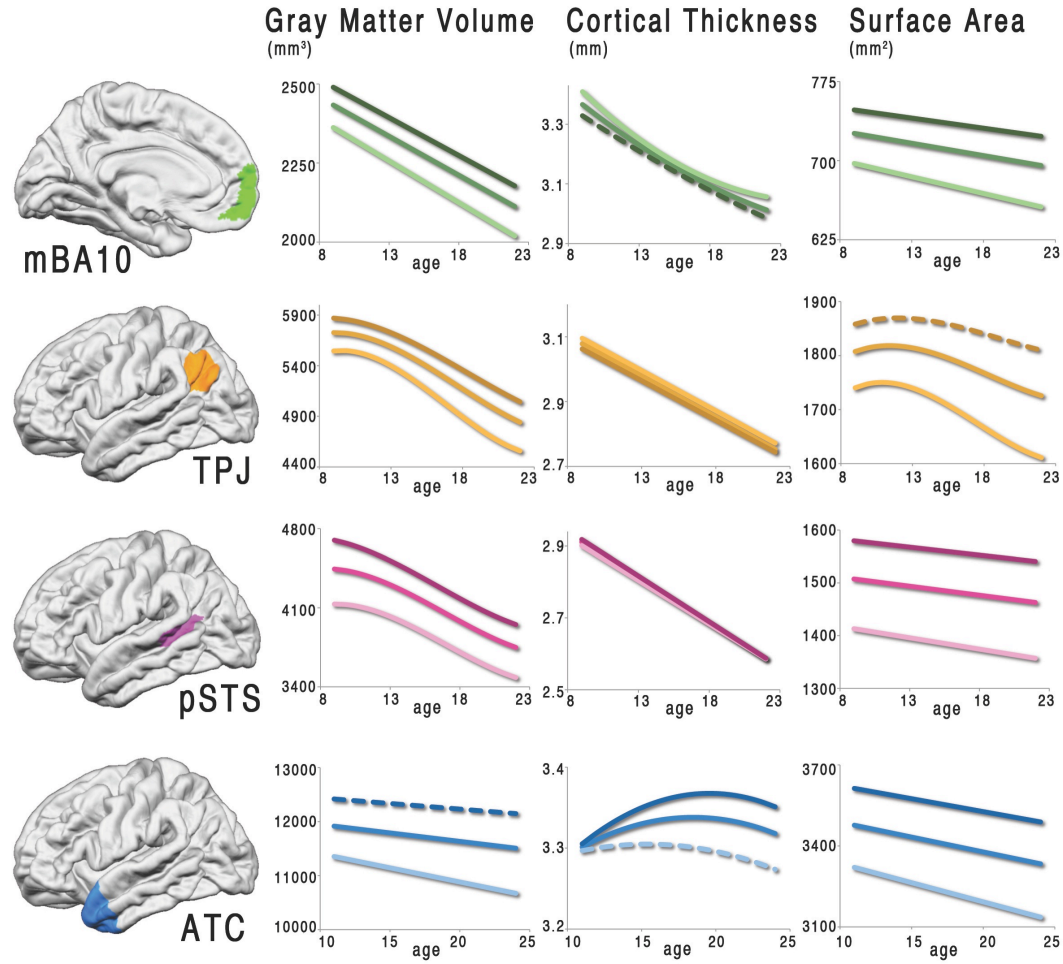


**Figure 5.4. Best fitting models for the left hemisphere only**. The best fitted models for all participants are shown for each region of interest measured on the left hemisphere only. Models are fitted to the middle 80% of the sample (ages 9–22 for mBA10, TPJ and pSTS; ages 11–24 for ATC). The lighter lines show the fitted models applied to females only, and the darker lines show the fitted models applied to males only. Solid lines indicate the fitted model was significant $p < 0.05$, whereas dashed lines indicate the fitted model was not significant ($p \geq 0.05$).

### 5.3.5 Sex Differences

Sex differences were observed in grey matter volume and surface area, but not in cortical thickness, for all ROIs. Grey matter volumes were larger across the age span studied for males than females in all regions: mBA10 (LR = 34.68, $p <$ .0001), TPJ (LR = 33.41, $p <$ .0001), pSTS (LR = 38.10, $p <$ .0001), and ATC (LR = 67.55, $p <$ .0001). Similarly, surface area was greater across the age span studied in all regions: mBA10 (LR = 53.83, $p <$ .0001), TPJ (LR = 42.26, $p <$ .0001), pSTS (LR = 41.30, $p <$ .0001), and ATC (LR = 55.67, $p <$ .0001). I

observed one gender by age interaction for TPJ surface area (LR = 9.89, $p < .02$), with females showing an earlier decrease in surface area before males. No differences in cortical thickness were observed between the sexes in the combined hemispheres and in the individual hemispheres. Left and right hemispheres showed the same effects as the combined hemispheres for mBA10, TPJ, pSTS and ATC, except the interactive effect for surface area in the TPJ was not observed in either individual hemisphere.

## 5.4 Discussion

The aim of this study was to investigate the structural development of the social brain network across adolescence using data from the largest longitudinal pediatric neuroimaging sample (288 participants; 857 scans; ages 7–30 years). Grey matter in mBA10, TPJ, and pSTS was at its highest volume in late childhood, and decreased from this point into adulthood. However, grey matter in the ATC continued to increase in volume until early adolescence before decreasing into adulthood. Similarly, cortical thickness in mBA10, TPJ and pSTS decreased linearly across adolescence, whereas cortical thickness in the ATC followed a quadratic trajectory increasing until early adulthood. Surface area for each region followed a cubic trajectory, reaching its highest level in early or pre-adolescence before decreasing into the early twenties. Differences in grey matter volume and surface area, but not in cortical thickness, were observed between female and male participants. Males displayed larger cortical volumes and greater surface area than females across all ROIs. Differences in developmental trajectories were only observed for the surface area of the TPJ, which reached the highest level in late childhood for females, but in early adolescence for males. As grey matter volume is the product of surface area and cortical thickness, it may be

that the sex differences observed in grey matter volumes are driven by differences in surface area rather than cortical thickness.

### 5.4.1 The social brain network

While the co-activation of the regions examined in the present study has been demonstrated in many social cognitive fMRI experiments, the individual contributions of these anatomically distinct regions to social cognitive processes is still under debate. Electrophysiological and fMRI studies consistently report the involvement of the pSTS in the perception of biological motion and eye gaze (Puce & Perrett, 2003), and in grasping the intentionality and appropriateness of biological motion (Pelphrey et al., 2004). It may be that the pSTS is involved in decoding complex social gestures conveyed through eye gaze and body movement. The TPJ, while in close anatomical proximity to the pSTS, is involved in different aspects of social cognition. It is suggested that the TPJ is activated specifically in situations when one is inferring the mental states of others, rather than just information known about another (Saxe & Kanwisher, 2003; Saxe et al., 2009). In contrast, mBA10 is activated in multiple conditions: when inferring the mental states of others, when reflecting on knowledge of another's traits, and when reflecting on the traits of oneself (C. D. Frith, 2007). In this paper, Chris Frith proposed that the underlying similarity between tasks that activate mBA10 is their involvement in handling communicative intentions, which requires a second order representation of mental state, whether our own or another's. A combination of lesion, non-human primate and fMRI studies has prompted researchers to theorise the involvement of the ATC in interpreting social narratives (Olson et al., 2013), and processing social scripts (C. D. Frith, 2007; U. Frith & Frith, 2003).

Many of the ROIs followed similar structural trajectories, with mBA10, TPJ and pSTS displaying the greatest volume grey matter during childhood, followed by a steady decrease in adolescence before leveling off in the early twenties. However, the ATC showed a different trajectory, increasing in grey matter volume until adolescence, after which slowly decreasing until leveling off in the mid-twenties. It is unclear why the ATC would continue to increase in grey matter volume until early adolescence. This area of the cortex contains important linkages to both the mPFC and limbic structures (e.g., amygdala, hippocampus) via the uncinate fasciculus, which is one of the last white matter tracts to reach maturity (Lebel et al., 2008). Perhaps the relatively late myelination of ATC projections allows a longer window for learning complex social information. Future investigations that measure white matter in social brain regions are needed to determine the role of white matter maturity (i.e., axonal caliber, myelination) in the development of these regions. Despite differences in the timing and tempo of grey matter volume decline between regions of the social brain, each region continues to change across adolescence before relatively stabilising in the early twenties. This protracted development supports the idea of adolescence as a sensitive period for neural changes in areas of the brain involved in social cognition.

### 5.4.2 Underlying anatomy and histology

Until recently, most structural MRI studies of the developing brain have examined only grey and white matter volumes in relatively large regions. Grey matter volume itself is the product of cortical thickness and surface area, which are influenced by distinct genetic (Panizzon et al., 2009; Winkler et al., 2010), evolutionary (Rakic, 1995), and cellular (Chenn & Walsh, 2002), processes, in addition to being phenotypically distinct (Winkler et al., 2010). Grey matter

volume is more correlated with, and genetically and environmentally related to, surface area than cortical thickness (Winkler et al., 2010). Differences in surface area are pronounced across species (Hill et al., 2010; Rakic, 1995), whereas cortical thickness is highly conserved in comparison (Fish, Dehay, Kennedy, & Huttner, 2008; Roth & Dicke, 2005).

The dissimilarity of cortical thickness and surface area growth across late childhood and adolescence is observable in the results of this study. Surface area is much more variable than cortical thickness between individuals (Figure 5.5). Perhaps the combination of decreasing linear trajectories in cortical thickness and subtle cubic trajectories in surface area observed in mBA10, TPJ and pSTS contribute to the earlier inflection (and more profound decrease) in grey matter volume trajectories observed in this study. In contrast, the continuing increase in cortical thickness, and gradual decrease in surface area, of the ATC shapes the grey matter trajectory to resemble the surface area trajectory.

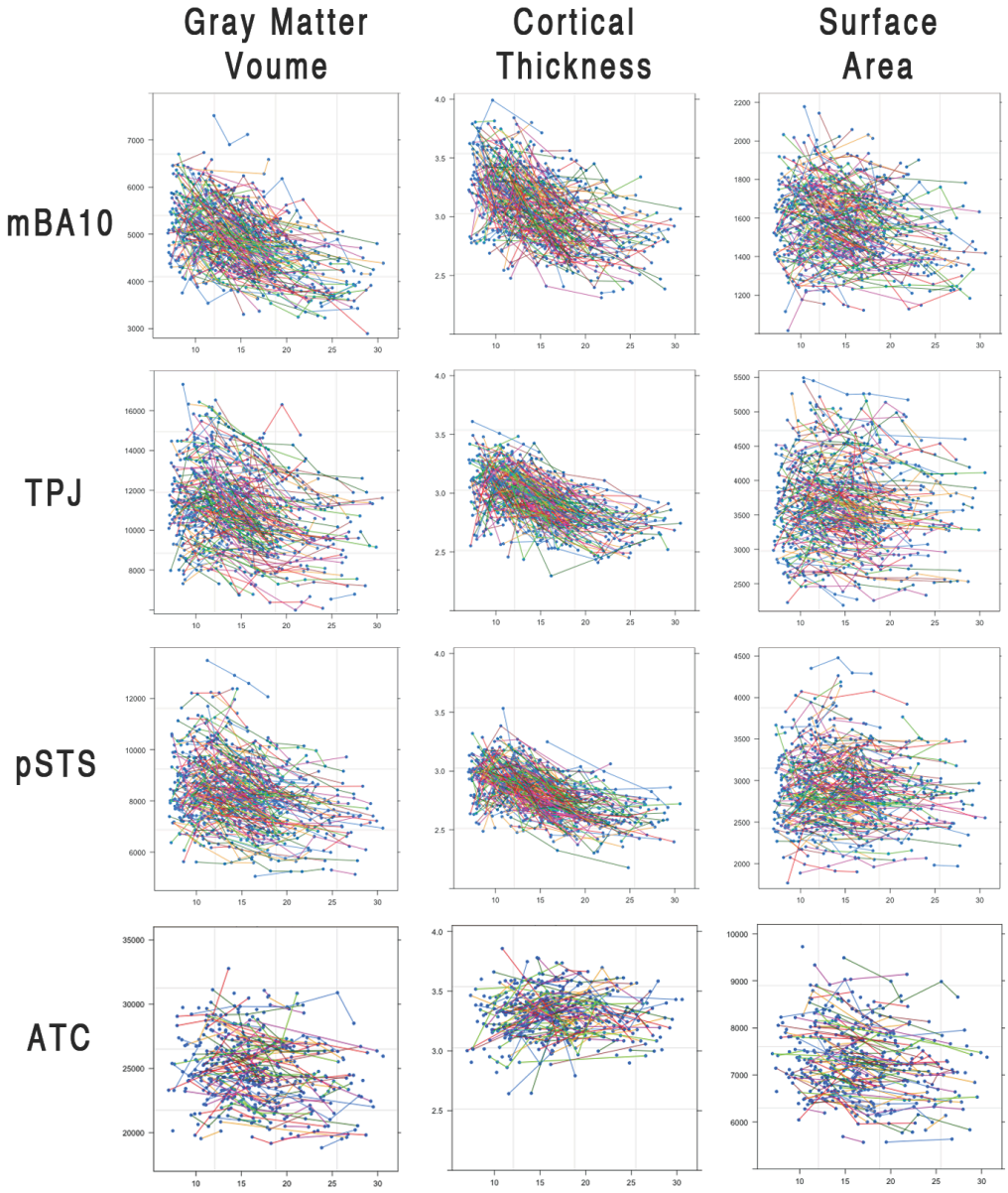


**Figure 5.5. Scatter plots of all participants for each measure (combined hemispheres) of each region of interest.** There are 288 individuals and 857 scans represented in the mBA10, TPJ and pSTS graphs, and 221 individuals and 447 scans represented in the ATC graphs.

The underlying mechanisms associated with a reduction in grey matter volume are still debated (See Chapter 2). Despite these limitations, it is thought that reductions in grey matter volume may reflect synaptic reorganisation and/or increases in white matter integrity. Histological studies of postmortem human brain tissue support the idea that association cortices continue to undergo synaptic pruning across adolescence (Huttenlocher & Dabholkar, 1997; Petanjek et al.,

2011), although the regions examined in these studies do not include the regions included in the present analysis. There is also histological evidence for an extended period of myelination in association cortices, continuing well into the twenties (Yakovlev & Lecours, 1967).

### 5.4.3 Relationship between structure and function

While the present study is the first to describe how areas of the social brain develop *structurally* across ages 7–30 years, there have been a number of fMRI studies that show functional changes in the social brain during this period (see Burnett, Sebastian, Cohen Kadosh, & Blakemore, 2011 for review). Many of these studies report decreases in dorsal mPFC recruitment between adolescence and adulthood during social cognitive tasks (Blakemore et al., 2007; Burnett et al., 2009; Goddings et al., 2012; Pfeifer et al., 2007, 2009; Sebastian et al., 2011; Wang et al., 2006). Why adolescents would recruit the mPFC, an area involved in decoding communicative intent and second order mental state representation, more than adults in social cognitive tasks is still a topic of investigation. It has been suggested that the decrease in recruitment of the mPFC across adolescence may relate to changes in neuroanatomy or maturing neurocognitive strategies (Blakemore, 2008). Likewise, the protracted structural development of the PFC is often interpreted as reflecting the relative neuroplasticity of this region during adolescence. This suggests that structural and functional changes in similar brain regions are co-occurring across development. This is supported by a study that correlated cortical grey matter thickness and functional brain activity in typically developing children performing an orthographic processing task (Lu et al., 2009). The authors of this study found that increased activation correlated with mature brain morphology in the same region, and that both of these measures correlate

with performance even after accounting for age. However, this study did not involve social cognition, and future developmental studies may begin to characterise the relationship between structural and functional changes by recording structural measures as a potential covariate in fMRI analysis, as some have already begun to do (Cohen Kadosh, Johnson, Dick, et al., 2012). This study demonstrated that both age-related and performance-related fMRI activation during a face processing task correlated with structural changes in some, but not all, of the same brain regions (Cohen Kadosh, Johnson, Dick, et al., 2012). Another study found that individual differences in grey and white matter volumes could not account for the age-related changes in fMRI activation during a relational reasoning task (Dumontheil, Houlton, et al., 2010). These mixed results suggest that age-related changes in BOLD signal do not entirely reflect structural maturation, and may instead reflect the maturation of neurocognitive strategies.

### 5.4.4 Limitations

The present analysis does not correlate brain structure with social cognitive skills. By correlating structural brain development trajectories in the social brain with social cognitive skills, future studies could characterise inter-individual differences in brain development as they relate to social cognition. It may be that extreme variations in tempo or timing of social brain development correlate with disorders of social cognition (e.g., autism spectrum disorders). However, as it is currently difficult to disentangle genetically pre-programmed developmental changes from those that are triggered by changes in the environment, it may not be possible to speculate on how social cognitive development influences the developmental changes occurring in the brain across development and vice versa.

The current study did not examine how puberty affected the observed structural brain development trajectories. As previous studies have found relationships between pubertal maturation changes in brain structure across adolescence (Bramen et al., 2012; Goddings et al., 2013; Peper & Dahl, 2013), it would be informative to explore the influence of puberty on the structural trajectories of these social brain regions.

Compared to most of the rest of the cortex, the regions of the social brain examined in the present study undergo slightly more protracted development (Tamnes, Walhovd, Dale, et al., 2013). However, it is worth noting that the lateral temporal cortex and the dorsolateral prefrontal cortex also show similarly protracted developmental trajectories (Tamnes, Walhovd, Dale, et al., 2013), suggesting that structural changes in these regions might also be related to cognitive development in adolescence. Indeed, the structural development of fronto-parietal regions has been linked to working memory development between ages 8-22 years (Tamnes, Walhovd, Grydeland, et al., 2013).

To further describe how regions of the social brain develop across adolescence, it would be beneficial to use structural and functional connectivity analytic methods. These methods illustrate how each region within the network communicates with the others, and changes in connectivity strength may reflect maturing neurocognitive strategies. Although previous fMRI studies have shown that recruitment of specific regions of the social brain changes across development, it is unclear how these regions interact during this period of time. As various brain networks have been shown to change in both organisation and connectivity

strength across adolescence (Fair et al., 2009), the social brain network may also undergo reorganisation during this period.

Finally, I would like to address the issue of quality control in structural MRI studies (discussed in greater depth in Chapter 2). This large sample included high quality structural MRI volumes that had been rated for motion and artefact. However, 48% of the cortical reconstructions for these high quality scans failed the FreeSurfer pipeline for one region only, the ATC. It is important to note that this is not a problem with FreeSurfer alone, but also other cortical reconstruction software. Many structural MRI investigations do not visually inspect cortical reconstructions, which could introduce substantial noise in the data, especially in the ATC. Based on these findings, I would recommend all future structural MRI investigations to include a second step in their quality control process, visual inspection of the cortical reconstructions, and to include the details of this process in their methods section.

## 5.5 Conclusion

The social brain network continues to develop structurally across adolescence before relatively stabilising in the early twenties. This protracted development lends support to the theory that adolescence is a sensitive period for neural changes in areas of the brain involved in social cognition. It is likely that convergence across multiple methodologies will help us understand how the social brain develops across adolescence.

# Chapter 6 Multitasking during social interactions in adolescence and early adulthood

## 6.1 Introduction

The ability to navigate social interactions continues to develop throughout human adolescence (reviewed in Chapter 1). For both adolescents and adults, many social interactions involve multitasking, such as keeping track of extraneous information whilst engaging in a conversation or remembering a phone number while taking directions from someone. Social interactions involve attending to social cues and often require taking a perspective that differs from one's own. Previous work has shown that the tendency to take a different perspective in social interactions continues to increase during adolescence and into young adulthood (Dumontheil, Apperly, et al., 2010). However, it is unknown whether the ability to process social cues, or take a different perspective, is affected by multitasking during social situations, and if this relationship changes across development. In the current study, I examined how keeping track of non-social information affects the ability to attend to social cues and adopt another person's perspective during social interactions, in a group of adolescents and young adults.

Whilst attending to social cues is largely automatic (Spunt & Lieberman, 2013), taking another person's perspective when it differs from one's own requires inhibiting our own, egocentric, perspective (Surtees & Apperly, 2012). For example, telling a story to a friend requires keeping track of any background information that she might not know. As humans are susceptible to *epistemic egocentrism* (Royzman, Cassidy, & Baron, 2003), inhibiting an egocentric perspective is effortful and requires cognitive resources for executive control,

such as working memory (Apperly et al., 2010b). It is possible to measure the availability of cognitive resources in an individual by assessing their working memory (WM) capacity. It is also possible to experimentally manipulate the availability of cognitive resources in an individual by asking them to simultaneously perform a task that taxes their WM capacity (cognitive load). Previous studies have shown that adults with higher WM capacity are better at inhibiting their egocentric perspective in live social interactions than individuals with lower WM capacity, and that this ability is disrupted in both groups when placed under high cognitive load (Lin, Keysar, & Epley, 2010). These results suggest that multitasking during a social interaction task would impair performance only when cognitive resources are sufficiently taxed. As both the tendency to take someone else's perspective (Dumontheil, Apperly, et al., 2010), and the ability to manipulate information in WM, are still developing in adolescence (Luciana, Conklin, Hooper, & Yarger, 2005; Luciana & Nelson, 2002), I hypothesised that adolescents would be more affected by cognitive load than adults when keeping track of other's perspectives during social interactions.

The present study examined how the availability of cognitive resources affects multitasking during social interactions in adolescents and adults. The present study's multitasking procedure required participants to carry out two tasks (one social and one non-social) simultaneously. The social task, called the Director Task (Figure 6.1), required participants to interpret instructions from an avatar (called the director) to decide which object to move in a shelf array (Keysar et al., 2000). On half of the trials, the director's perspective was different from that of the participant, and participants needed to take into account the director's different perspective when deciding which object to move. The non-social task was a visual

WM task in which two-digit numbers were visually presented before each Director Task stimulus. This non-social WM task also allowed for the manipulation of the level of cognitive load by requiring participants to remember either one two-digit number (low load) or three two-digit numbers (high load). At the end of each trial, we assessed the participants' ability to keep the number(s) in mind during the Director Task in order to obtain a measure of how successful participants were at multitasking during the social interaction. A matched rule-based variant of the Director Task which did not use social cues or necessitate perspective taking was used to differentiate between a general impact of cognitive control demands on performance from effects that specifically impact the social components of the task, i.e. using social cues and taking someone else's perspective into account.

This study also measured how natural variation in cognitive resources (assessed by WM capacity) related to multitasking performance. Participants completed a verbal reverse digit-span task as a measure of WM capacity (WM score) to assess individual differences in baseline cognitive resources. Finally, as the tendency to take a different perspective in social interactions continues to increase during adolescence and into young adulthood (Dumontheil, Apperly, et al., 2010), this study assessed how individual differences in trait perspective taking related to multitasking performance.

## 6.2 Methods

### 6.2.1 Participants

I tested 30 female adults and 37 female adolescents. Any outliers (determined by interquartile range) in individual traits were excluded: one adolescent for low IQ

and one adolescent for low trait perspective taking. Two adults and two adolescents were excluded for performing lower than chance (33% accuracy) on at least one task condition. The entire dataset before exclusion criteria were applied and the analysis script detailing the exclusion procedure are available online (http://dx.doi.org/10.6084/m9.figshare.1098780). Data from 33 adolescents (11–17 years, mean age: 14.5 ± 1.7) and 28 adults (22–30 years, mean age: 25.2 ± 2.3) were included in the analysis (Table 6.1). Participant groups did not differ in nonverbal IQ, measured by the matrix reasoning subtest of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). Adult participants were recruited through the UCL Psychology subject pool and adolescents through local advertisements. Written informed consent and assent to participate in the study were obtained from parents/adult participants and children respectively, and participants were compensated for their time. The study was approved by the local Research Ethics Committee.

| | Adolescents | Adults |
|---|---|---|
| Number of Participants | 33 | 28 |
| Age Range (years) | 11.3 – 17.8 | 22.4 – 30.0 |
| Mean Age (years) (SD) | 14.5 ± 1.7 | 25.2 ± 2.3 |
| Nonverbal IQ (SD) | 108.6 ± 8.9 | 108.3 ± 8.7 |
| WM Score* (SD) | 8.7 ± 3.7 | 11.6 ± 5.1 |
| Trait Perspective Taking* | 15.5 ± 4.4 | 18.8 ± 3.6 |

* indicates significant differences between adolescent and adult groups at $p < 0.01$

**Table 6.1. Participant demographics (all female).**

### 6.2.2 Procedure

Participants completed four tasks in one laboratory visit. First, participants completed an adapted version of the Director Task (from Dumontheil et al., 2012;

Figure 6.1) with an embedded working memory (WM) Task component. Afterwards, participants completed a verbal reverse digit-span task to obtain a measure of trait verbal WM capacity (WM Score), and the Interpersonal Reactivity Index questionnaire to obtain a measure of trait perspective taking (TPT; Davis, 1980), and finally the matrix reasoning subtest of the WASI (Wechsler, 1999).

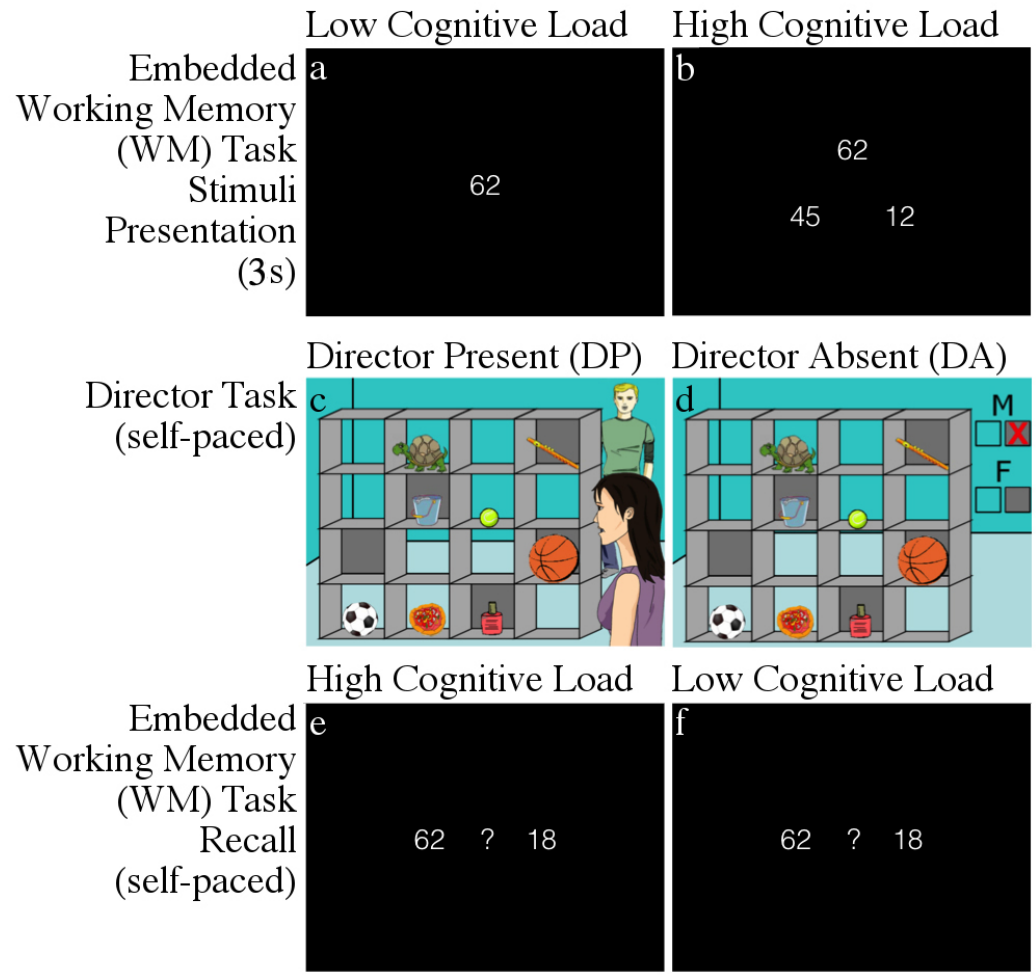


**Figure 6.1. Presentation of multitasking paradigm.** For each trial, participants were first presented with either (a) one two-digit number (low load) or (b) three two-digit numbers (high load) for 3s. Then participants were presented with the Director Task stimuli, which included a social (c) and non-social control condition (d). In this example, participants hear the instruction: "Move the large ball up" in either a male or female voice. If the voice is female, the correct object to move is the basketball, because in the DP condition the female director is standing in front of the shelves and can see all the objects, and in the DA condition, the absence of a red X on the grey box below the "F" indicate that all objects can be moved by the participant. If the voice is male, the correct object to move is the football, because in the DP condition the male director is standing behind the shelves and therefore cannot see the larger basketball in the covered slot, and in the DA condition the red X over the grey box below the "M" indicates that no objects in front of a grey background can be moved. After selecting an object in the Director Task, participants were presented with a display of two numbers, one of which corresponding to

the only number (e), or one of the three numbers (f), shown to them at the beginning of the trial. Participants were instructed to click on the number they remembered being shown at the beginning of the trial.

### 6.2.3 Director Task with embedded WM Task

The Director Task with embedded WM Task followed a 2 × 2 × 2 factorial design, with three within subject factors Cognitive Load (low or high), Condition (director present or director absent), and Perspective (same or different).

Each trial started with presentation of the WM Task stimulus: either one two-digit number (low cognitive load; Figure 6.1a) or three two-digit numbers (high cognitive load; Figure 6.1b) were shown for 3s.

Following the number display, participants were presented with the Director Task stimuli (48 total stimuli). These stimuli consisted of sets of 4×4 shelves with objects located in half of the slots. Five of the shelves had a grey background. On each trial, participants were given an instruction, by either a female or a male voice, to move one of the eight objects to a different slot in the shelves. The instructions referred to an object that was one of three exemplars in the shelves (e.g., the ball). In the Director Present (DP) condition, the display included two directors, one female and one male. One of them stood behind the shelves, facing the participant, whereas the other stood on the same side of the shelves as the participant (Figure 6.1c). Out of the three exemplars of the object, one was always located in a slot with a grey background, not visible to the director standing behind the shelves. Consequently, only one of two objects could correspond to the heard instruction ("Move the large ball up"), depending on the director's viewpoint: the object in the closed slot if the director stood in front of the shelves, or the object in the clear slot if the director stood behind the shelves. Participants

were instructed to use the position of the speaking director in order to determine which object to select and move. On half of the trials, the perspective of the director was the same as that of the participants (i.e. the director was standing in front of the shelves), on the other half the perspective of the director was different (i.e. the director was standing behind the shelves). Therefore, participants had to consider the director's position and perspective to determine the correct object to move.

In the Director Absent (DA) condition, the auditory stimuli, object arrays and general instructions were the same as in the DP condition, but instead of directors alongside the shelves, there were two letters ("M" and "F") with two boxes underneath each letter (Figure 6.1d). These boxes served to indicate which boxes the participants could move objects from, depending on whether the male ("M") or the female ("F") gave the instruction. For example, the display in Figure 6.1d informs participants that if the male is speaking they cannot move objects located in slots with a grey background (because the grey box is crossed out), while if the female is speaking, they can move objects located in clear slots and those in slots with a grey background. These rules had precisely the same consequences as the position of the director in the DP blocks. Although perspective taking was not involved in the DA condition, for brevity I describe the manipulation of which object was the correct one to move (e.g. the largest of the three balls or the second largest visible to the director standing at the back/not in a slot with a grey background slot) as 'perspective' across DP and DA conditions for the analysis and results.

To vary the social and/or executive demands of task, half of the Director Task trials included only one possibly correct object. In these trials, participants were shown arrays in which a unique target object was displayed in an open slot. In these trials the director's perspective in the DP condition, or the position of the X in the DA condition, made no difference to the correct interpretation of the instructions, and thus, participants could use their own perspective to select the appropriate object on all trials.

Each participant performed 16 blocks of 12 trials for a total of 192 trials. The blocks were mixed and counterbalanced for the DP and DA condition. The same displays were used for the DP and DA conditions. The position of the directors (or the crossed box in the DA condition) was constant within blocks. However, cognitive load (low or high), the number of possibly target objects (1 or 3), and the gender of the speaker (female or male), varied by trial.

For each Director Task trial, the auditory instructions were presented with the visual stimulus over a period of 2.2s, after which the visual stimulus remained on the screen until the participant made a selection – this was self-paced. Participants were instructed to listen to the instructions, select the correct object, then click-and-drag that object to the correct slot. Reaction times (RTs) were calculated as the delay between the presentation of the visual stimulus and the pressing of the mouse button. Accuracy on this task only considered which object was selected, and not whether it was moved to the correct slot, as the object selection is the measure of interest in this task.

After participants completed the Director Task portion of the trial, they were presented with a display of two numbers, one of which corresponded to the only number (low cognitive load; Figure 6.1e), or one of the three numbers (high cognitive load; Figure 6.1f), shown to them prior to the Director Task trial. Participants were instructed to click on the number they remembered being shown to them at the beginning of the trial.

### 6.2.4 Backward Verbal Digit Span Task

Participants were instructed to repeat back sequences of three to seven numbers read aloud by the experimenter in reverse order. Numbers for the sequences were randomly generated in MATLAB and were read aloud by the experimenter at 1s intervals. After a practice trial with a sequence of two numbers, the sequences of numbers progressed by sets of four between three-span to six-span, whereas there were only two seven-span sequences. Participants had to remember two of the four sequences within each set to move onto the next set, or else the task was terminated. If a participant wrongly remembered the last sequence of one set and the first sequence of the next set, the task was terminated. Each participant's WM score was calculated as the number of correctly recalled sequences.

### 6.2.5 Interpersonal Reactivity Index (IRI) Questionnaire

The IRI consists of 28 self-reflective questions using 5-point scales, divided into four subscales (Davis, 1980). For this study, I only used the score obtained on the Perspective Taking subscale.

### 6.2.6 Data analysis

I used mixed-effects modelling to determine what factors best predicted multitasking performance. Accuracy was determined on a trial-by-trial basis, where a trial was considered accurate only if participants correctly performed both the Director Task and embedded WM Task. As the main interest was performance during social interactions, and not recall of non-social information, I analysed Director Task RT (correct trials only).

| Global Models |
|---|
| 1. Group * Cognitive Load * Condition * Perspective |
| 2. Group * Cognitive Load * Condition * Perspective + WM Score |
| 3. Group * Cognitive Load * Condition * Perspective + Trait Perspective Taking |
| 4. Group * Cognitive Load * Condition * Perspective + WM Score + Trait Perspective Taking |
| 5. Group * Cognitive Load * Condition * Perspective + Combined Traits |
| * indicates main and interactive effects were explored between variables.<br>+ indicates only main effects were explored between variables. |

**Table 6.2. Five Global Models.** The five global models tested for each outcome of interest. When each of these models went through the automated search procedure, the potential main and interactive effects of each variable were compared. For example, the global search procedure for Global Model 1 compared the potential main and interactive effects for Group, Cognitive Load, Condition and Perspective. The difference between Model 4 and Model 5 is that Model 5 does not allow for individual main effects for Trait Perspective Taking and WM Score, but instead only looks at the potential effects of an interaction between these two traits (Combined Traits).

I used the lme4 package in R (Bates, Maechler, & Bolker, 2013) to perform a linear mixed-effects analysis on the relationship between the factors of interest and multitasking performance (accuracy and RT). The factors of interest included three within-subject factors from the task: cognitive load (low vs. high), condition (DA vs. DP), perspective (same vs. different); two individual traits: WM score and TPT; and one between-subjects factor, group: (adolescents vs. adults). As I hypothesised an interaction between WM capacity and TPT would relate to the task, I included a combined measure of these two individual traits by calculating

and summing the ratios of TPT and WM Score (Combined Traits). I determined which factors best predicted performance for the measures of interest by testing global models including the factors of interest as fixed effects. Each model included a random intercept for each participant. Because of computational limitations, I performed a two-step procedure that involved five global models (Table 6.2). First, all possible combinations of the variables within each of the five global models were tested using an automated model selection procedure (MuMIn1.9.0; Barton, 2013). Models were ranked using the Second-order Akaike Information Criterion (AICc; Burnham & Anderson, 2002). Second, the best fitting model for each of the five global models were compared and ranked using AIC and likelihood ratio tests. All p-values reported in the main text were obtained by likelihood ratio tests comparing the best fitting model against a baseline model that includes only the random effects and not the fixed effects of interest. All data, analysis scripts and results are available online: http://dx.doi.org/10.6084/m9.figshare.1098780.

### 6.2.7 Excluded trials

All errors were analysed and categorised. Trials in which errors were not specific to experimental instructions (e.g. the participant clicked outside of the shelf array) were excluded from the analysis (139 trials). Of the 48 stimuli, two were excluded because of deviant errors rates. I excluded trials in which participants responded faster than 600ms (3 trials), or slower than 20s (3 trials) during the Director Task. As trials with unique target objects were only included in the present study to provide variety in the task instructions, I did not include these trials in the analyses. I analysed a total of 5,539 trials.

## 6.3 Results

### 6.3.1 Individual traits

Mean scores on the Backward Verbal Digit Span Task (WM score) and Perspective Taking subscale of the IRI (TPT) are reported in Table 6.1. Overall, adolescent participants had lower WM scores than adults ($p < 0.01$). Adolescent participants also reported having significantly lower TPT than adults ($p < 0.01$).

| | **Accuracy** | | | |
|---|---|---|---|---|
| Fixed effects | Estimate | SE | *Z*-value | *p*-value |
| **Intercept** | 0.80 | 0.32 | 2.49 | **0.013** |
| Group | -0.33 | 0.19 | -1.71 | 0.087 |
| **Cognitive Load** | -1.12 | 0.09 | -11.92 | **<0.001** |
| **Condition** | 0.42 | 0.10 | 4.36 | **<0.001** |
| Perspective | 0.11 | 0.09 | 1.18 | 0.237 |
| **Combined Traits** | 0.83 | 0.28 | 2.93 | **0.003** |
| **Group × Cognitive Load** | 0.39 | 0.14 | 2.83 | **0.005** |
| **Condition × Perspective** | -0.27 | 0.13 | -2.01 | **0.045** |

| | **Director Task RT** | | | |
|---|---|---|---|---|
| Fixed effects | Estimate | SE | *t*-value | *p*-value |
| **Intercept** | 3844.80 | 83.70 | 45.94 | **<0.001** |
| **Cognitive Load** | 138.10 | 66.30 | 2.08 | **0.037** |
| **Condition** | -305.90 | 61.40 | -4.99 | **<0.001** |
| **Perspective** | 576.30 | 60.70 | 9.50 | **<0.001** |
| **Cognitive Load × Condition** | -275.70 | 91.40 | -3.02 | **0.003** |
| Cognitive Load × Perspective | 35.30 | 91.60 | 0.39 | 0.700 |
| Condition × Perspective | -33.80 | 85.90 | -0.39 | 0.694 |
| **Cognitive Load × Condition × Perspective** | 287.60 | 127.20 | 2.26 | **0.024** |

**Table 6.3. Best fitting models for multitasking Accuracy and Director Task RT from correct multitasking trials only.** The table displays the linear mixed model parameter estimates and standard errors (SE) of each fixed effect included in the best fitting model. Model parameters reflect the influence of the following: Group: effect of adults completing the task compared to adolescents (baseline); Cognitive Load: effect of high cognitive load

compared to low cognitive load (baseline); Condition: effect of Director presence compared to Director absence (baseline); Perspective: effect of different perspective compared to same perspective (baseline); Combined Traits: the summed ratios of TPT and WM Score. Significant fixed effects are highlighted in bold. Z-values are reported for binomial models (accuracy) and t-values are reported for linear models (RT).

### 6.3.1 Accuracy

Details of the best fitting models for accuracy and RT are included in Table 6.3. The best fitting model for multitasking accuracy ($\chi^2(7)= 235$, $p < 0.001$) included the main effects of group (adolescents vs. adults), cognitive load (low vs. high), condition (DA vs. DP), perspective (same or different from the participant's perspective), and the combined traits of WM score and TPT, as well as interactions between condition and perspective (Figure 6.2a), and between group and cognitive load (Figure 6.2b). On average, all participants were less accurate when under high cognitive load, and when using non-social cues (DA condition) to guide decisions. The interaction between group and cognitive load revealed that although both age groups showed poorer accuracy under high cognitive load ($ps <$ 0.001), adolescents' multitasking accuracy was more affected by cognitive load than the adults' (Figure 6.2b). Across age groups, there was an interaction between condition and perspective (Figure 6.2a). In the DP condition, participants were marginally less accurate when the perspective was different from their own compared to when it was the same ($p = 0.06$), while perspective had no effect on accuracy in the DA condition ($p = 0.15$), i.e. when using non-social cues to guide decisions. Following the condition by perspective interaction by comparing DP and DA conditions in same or different perspective trials instead showed that participants were more accurate when using social cues to select the correct object compared to non-social cues ($p < 0.001$), but only when participants shared the same perspective as the director. There was no significant difference in accuracy ($p = 0.33$) between DP and DA conditions when participants had to inhibit their

own egocentric perspective to select the correct object. The combined traits measure of WM score and TPT was correlated with overall multitasking accuracy, in that a combination of higher WM score and higher trait perspective taking was associated with higher multitasking accuracy overall ($r = 0.33$, $p < 0.01$) (Figure 6.2c).

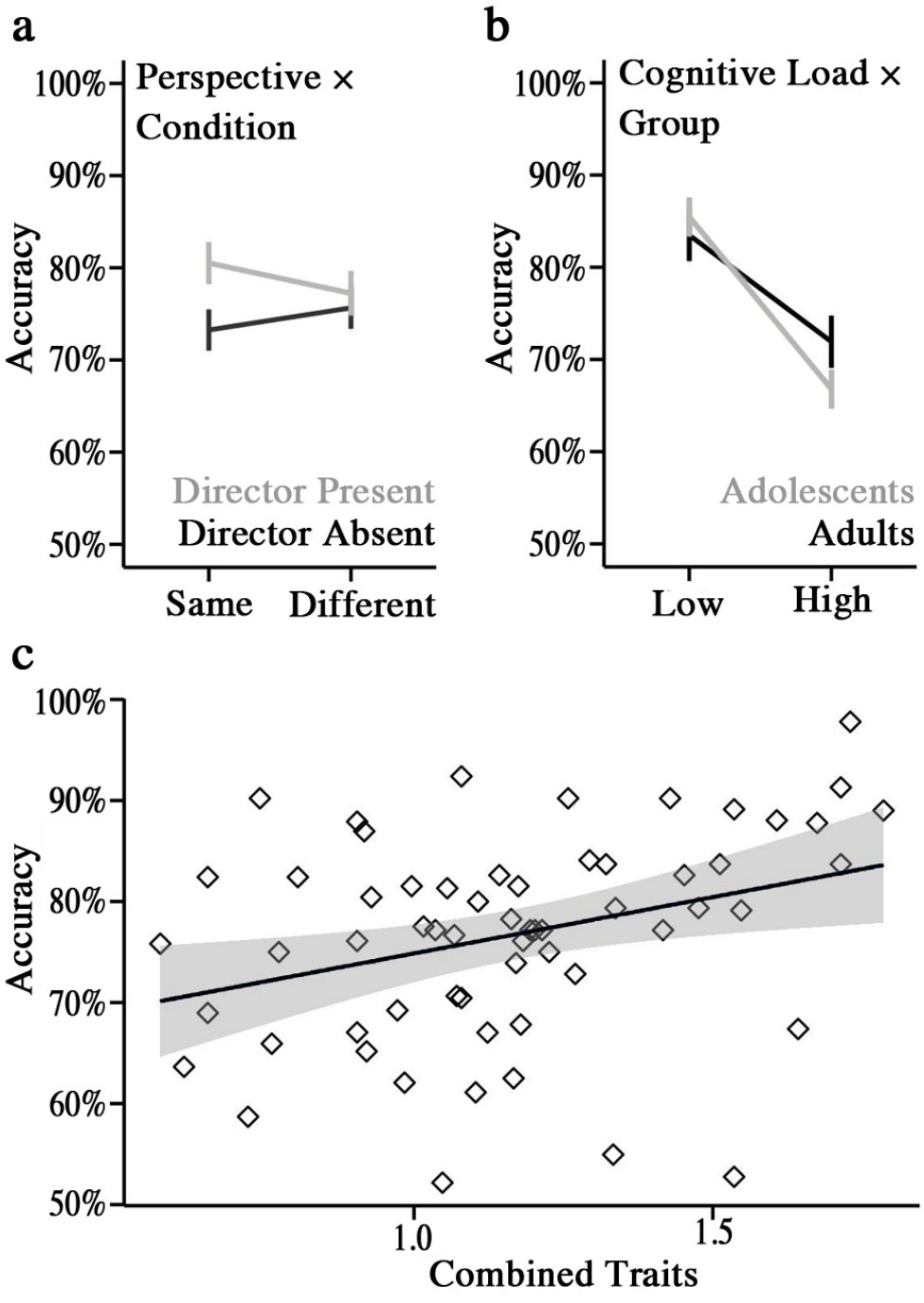


**Figure 6.2. Multitasking accuracy results.** (a) On average, there was an interaction between condition and perspective, driven by marginally ($p = 0.06$) lower accuracy when

using social cues (Director Present condition) to guide decisions when the perspective was different from their own, but no significant difference in accuracy ($p$ = 0.15) when using non-social cues (Director Absent condition) to guide decisions. Regardless of cognitive load, participants were more accurate when using social cues to select the correct object compared to non-social cues ($p < 0.001$), but only when participants shared the same perspective as the director. (b) On average, the adolescents multitasking accuracy was more affected by cognitive load than the adults. (c) The combined traits measure of WM score and TPT was correlated with overall multitasking accuracy ($r$ = 0.33, $p < 0.01$). Error bars represent 95% confidence intervals.

### 6.3.2 Reaction Time (RT)

I analysed RT data from the Director Task for correct multitasking trials. The best fitting model for RT during correct multitasking trials ($\chi^2(7)= 561$, $p < 0.001$) included the main effects of cognitive load, condition and perspective, as well as a two-way interaction between cognitive load and condition, and a three-way interaction between cognitive load, condition, and perspective (Figure 6.3). On average, participants were slower under high cognitive load ($p$ = 0.037), when using non-social cues (DA condition) to guide decisions ($p < 0.001$), and when they had to adopt a different perspective. In both the low cognitive load and high cognitive load conditions, participants were faster at the Director Task when using social cues to select the correct object than when using the non-social cues ($ps <$ 0.001). When using non-social cues (DA condition) to guide decisions, participants were slower under high cognitive load compared to low cognitive load ($p$ = 0.03), whereas cognitive load did not significantly affect RT for trials in which participants had to use social cues (DP condition) to guide decisions ($p$ = 0.30) (Figure 6.3a). However, the three-way interaction revealed a cognitive load effect on RT when participants had to take into account a different perspective specifically when using social cues to select the correct object. In the DP condition, there was a significant cognitive load × perspective interaction ($p <$ 0.001), which was not observed in the DA condition ($p$ = 0.60) where cognitive load had slowed RT across both perspectives. Following the significant

interaction in DP showed that when under high cognitive load, participants were slower when taking a different perspective compared when they did not have to take a different perspective ($p < 0.001$). The best fitting model did not include age group as a main or interactive effect for RT.

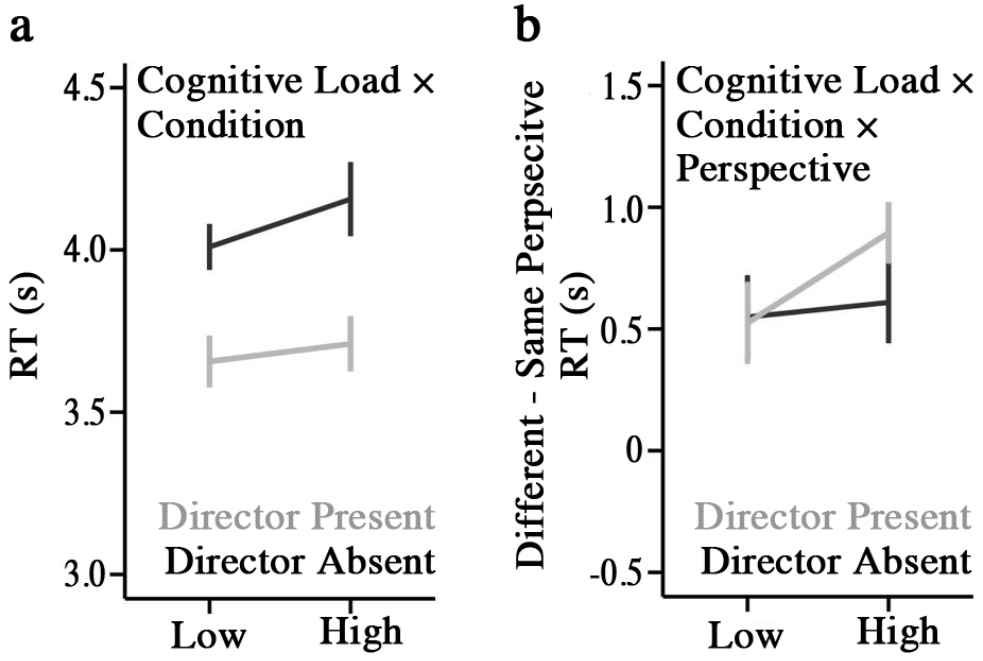


**Figure 6.3. Director Task RT results.** I analysed RT data from the Director Task for correct multitasking trials. (a) In both the low cognitive load and high cognitive load conditions, participants were faster at the Director Task when using social cues to select the correct object than when using the non-social cues ($p < 0.001$). When using non-social cues (Director Absent condition) to guide decisions, participants were slower under high cognitive load compared to low cognitive load ($p = 0.03$), whereas cognitive load did not seem to affect RT for trials in which participants had to use social cues (Director Present condition) to guide decisions ($p = 0.30$). (b) When under high cognitive load, participants were slower at selecting the correct object when taking a different perspective compared when they did not have to take a different perspective ($p < 0.001$), and this effect was present only when using social cues to select the correct object. Error bars represent 95% confidence intervals.

## 6.4 Discussion

In this study, I investigated how the availability of cognitive resources affects the ability to successfully perform a social interaction task whilst simultaneously keeping track of non-social information – a form of multitasking – in both adolescents and adults. Given the natural limitations of how much information

individuals can keep track of at once, I hypothesised that multitasking performance in the social interaction task would be diminished when participants had to simultaneously keep track of several pieces of non-social information (high cognitive load). The results of the present study were in line with this hypothesis, as participants in both age groups were less proficient at performing both the social and non-social task when they were under high cognitive load. Compared with adults, the adolescent group showed a greater decrement in performance when having to keep track of several pieces of non-social information whilst multitasking.

These results suggest that processing and using social cues to guide behaviour is relatively automatic when the partner in a social interaction shares the same perspective (see Figure 6.3a). Both adult and adolescent participants were, on average, faster and more accurate when using social cues to guide decisions. However, multitasking accuracy was impaired when participants had to inhibit their own egocentric perspective to select the correct object. While cognitive load did not differentially affect multitasking accuracy under different perspectives, it did affect how fast participants reacted in the social interaction task. Participants in both age groups were slower at taking another's perspective, compared to their own, when under high cognitive load. This effect was specific to social cues, suggesting that taking another's perspective is a cognitively taxing activity that can disrupt social interactions when one is simultaneously keeping track of several pieces of non-social information.

A previous study using a live version of the Director Task found that adults under high cognitive load made more errors during trials that required inhibiting their

egocentric perspective to select the correct item (Lin et al., 2010). However, unlike the present study, this previous study did not include a control condition (the Director Absent condition) that accounts for the general processing demands of inhibiting the prepotent response to select the distractor object. Therefore, the previous study was unable to address if the depletion of cognitive resources interacted specifically with the social processing demands of the Director Task (Lin et al., 2010). Although Lin et al. interpreted their results as providing evidence that cognitive resource availability affects the ability to use theory of mind during social interactions, without the control condition, it is not possible to interpret the results as specifically relating to the cognitive resources needed to take into account the perspective of another individual. It could be that the presence of a distractor object in general would impair a participant's performance. The present study tested the effects of cognitive load on processing social information by including a cognitive load manipulation and a control condition matched on the general processing demands of selecting a target among distracting stimuli (the Director Absent condition). Thus, this study was able to specifically measure the impact of social perspective taking, above and beyond inhibiting a prepotent response (i.e. egocentric perspective), on selecting the correct object. The present study showed that specifically taking another person's perspective when it differs from one's own necessitates cognitive resources that are depleted under cognitive load, and that this effect is not simply due to the general cognitive control demands required when choosing a target object in the presence of a distractor object.

I hypothesised that the natural variability between individuals in both cognitive resource capacity (WM capacity) and the tendency to take another's perspective

(trait perspective taking) would relate to performance on the multitasking paradigm. To test this hypothesis, I created a combined measure of these two traits and included it in the statistical model selection procedure. The best fitting model included this combined trait, suggesting that trait differences were able to explain multitasking performance above and beyond other task-related factors. This is not surprising, given that the present study's multitasking paradigm was a combination of two tasks that necessitated keeping track of non-social information and accurately taking another's perspective. This was true for both adolescents and adults.

As adolescence is a time when complex social cognitive skills are changing along with the social environment (see Chapter 1 for review), this study addressed how cognitive control abilities (i.e., the ability to manipulate information in WM) might influence the continued development of social navigation skills between adolescence and adulthood. An fMRI study that used a similar version of the Director Task found that adults recruited a network of fronto-parietal regions involved in cognitive control when inhibiting an egocentric perspective (across both the Director Present and Director Absent conditions) more than adolescents (Dumontheil et al., 2012). It might be that an increased recruitment of cognitive control capacities during social interactions between adolescence and adulthood can offset the potential decrement in multitasking performance when individuals are placed under high cognitive load.

Within the typical social environment, we are regularly faced with situations that require multitasking whilst engaging in a social interaction. Therefore, it is important to understand how simultaneously keeping in mind extraneous

information influences our ability to engage in a communicative task with another person. The results of the present study support the idea that adolescents are more sensitive to additional cognitive load requirements than are adults in multitasking situations. These findings suggest that adolescents might have difficulty in certain social situations in which adults perform without any problem, such as when having to keep track of extraneous information whilst also social interacting with another individual. Given that performance deficits resulting from multitasking interference effects occur only when an individual's cognitive resources are sufficiently taxed (Norman & Bobrow, 1975), it might be that the high cognitive load condition in this study was more taxing to adolescents than adults. Indeed, on average, the adult participants had greater WM capacity than the adolescent participants.

It is important to note that both adolescents and adults are affected by multitasking when engaging in social interactions that require taking another person's perspective. The results of the present study show that when participants had to keep track of only one piece of non-social information, they were just as fast responding to the avatar's directions regardless of the avatar's perspective. However, when keeping track of three pieces of non-social information, participants were significantly slower at responding to the avatar's directions when the avatar did not share the same perspective as the participant. These results suggest that the natural pace of social interactions, such as everyday conversations, could be disrupted when adolescents or adults are simultaneously keeping track of extraneous information.

In the current study, participants kept track of either one or three pieces of non-social information whilst also performing a referential communication task with a computer avatar. This task is akin to having a conversation with someone whilst in the middle of an unrelated task – such as programming an experiment or doing a classroom assignment – in which one must keep track of information not relevant to the current social interaction. The results showed a significant decrease in multitasking performance accuracy (~10% for adults and ~15% for adolescents) when participants had to remember three pieces, compared to one piece, of non-social information. This suggests that attempting to keep track of just a few pieces of non-social information during a social situation can be impairing to both the social interaction, and the later recall of the non-social information. Further, multitasking situations that some adults navigate effectively might be too difficult for some adolescents. These results might have implications for how adults who work with adolescents (e.g., teachers, mentors) structure activities with adolescents. For example, in-class group work might be particularly difficult for adolescents who are already struggling with the assignment topic.

# Chapter 7 How does Internet use affect the adolescent brain?

> 'For this invention will produce forgetfulness in the minds of those who learn to use it, because they will not practice their memory. Their trust in writing, produced by external characters which are no part of themselves, will discourage the use of their own memory within them.' Socrates

## 7.1 Summary

Twenty-five years have passed since the invention of the World Wide Web changed society by allowing unfettered access to the Internet. How this technological revolution has affected brain development continues to be an open question. There is particular concern about how Internet use is affecting the brains of adolescents. This brief systematic review discusses the possible effects of the Internet, as well as the behaviours and capabilities associated with its use, on the adolescent brain.

## 7.2 Introduction

Throughout history, adults have worried about the effects of new tools and technologies on human development. Socrates warned his students of the dangers associated with writing and Plato immortalised his views by writing them down in the dialogue Phaedrus (370 BCE) (see quote). Today, teachers voice similar concerns about the effects of Internet use on the cognitive abilities of students growing up with access to the World Wide Web (Purcell et al., 2012). Of the 2,462 American middle- and high-school teachers surveyed by the Pew Research Center, 87% felt that widespread Internet use was creating an 'easily distracted generation with short attention spans' and 88% felt that 'today's students have fundamentally different cognitive skills because of the digital technologies they

have grown up with'. Although teachers and other adults who spend their time with children and teenagers possess valuable observational knowledge about generational trends, it is unclear whether current scientific evidence supports these claims.

The focus of this chapter is to systematically consider how Internet use – a complex construct that encompasses multiple activities such as information gathering, entertainment, and communication through the medium of the World Wide Web – as opposed to other media use, might affect the adolescent brain.

The naturally malleable period of adolescence, which is often defined as beginning around puberty and ending when one obtains a relatively stable role in society, makes this a time of particular concern to adults. Agency and many cognitive skills increase during early adolescence, yet some skills (such as navigating the social world) continue to develop throughout the teen years. Likewise, the human brain undergoes profound changes in both its structure and its function during adolescence (reviewed in Chapter 1). Cellular studies of post-mortem brain tissue have shown high levels of dendritic spines in the prefrontal cortex in late childhood/early adolescence, with the number of spines reducing by almost half through the teenage years and into the third decade (Petanjek et al., 2011). Because experience partially determines what connections are kept and strengthened during this period of development, some adults are concerned that Internet use could be 'rewiring' the brains of individuals growing up online.

## 7.3 A systematic review of the literature

I conducted a literature search using the PubMED database to identify all

available peer-reviewed studies that contained the following three keywords: "adolescence" and "internet" and "brain". Specifically, my search was the following string: ("internet"[MeSH Terms] OR "internet"[All Fields]) AND ("brain"[MeSH Terms] OR "brain"[All Fields]) AND ("adolescent"[MeSH Terms] OR "adolescent"[All Fields] OR "adolescence"[All Fields] OR "teenage"[All Fields] OR "teenager"[All Fields]). As of 5 February 2014, 134 articles met this criteria. I then examined and categorised each of these 134 articles into the following four categories: Empirical, Review, Clinical, or Irrelevant (Figure 7.1). Two were classified as Empirical articles, as they contained analyses that could be used to understand how aspects of Internet use could be affecting adolescent cognition or brain measures (D. H. Han et al., 2011; Silk et al., 2012) (Table 7.1). Two were classified as Review articles, as they did not contain empirical research, but did address the issues related to Internet use and the developing brain (Choudhury & McKinney, 2013; Giedd, 2012) (Table 7.1). Twenty articles were classified as Clinical, as they were studies which assessed some aspect of internet use on the cognition or brain measures of individuals that have been diagnosed with a form of Internet Use Disorder (Table 7.2). The remaining 110 articles were classified as Irrelevant, as they did not address how aspects of Internet use could be affecting cognition or brain measures of individuals of any age (see Appendix 7.1 for full list of Irrelevant articles). Many of these irrelevant articles assessed the use of online-based therapies, or involved young people with head injuries.

One empirical article used a task that simulated a live Internet chatroom (Silk et al., 2012). Using this task, the study measured how adolescents aged 9–17 years reacted to peer acceptance or rejection. Although adolescents in this study were

more likely to direct their attention toward acceptance feedback and away from rejection feedback, they showed more emotional and cognitive reactivity (as measured by pupil dilation) to rejection feedback (Silk et al., 2012). The adolescents that reacted most strongly to the rejection feedback during the task were more likely to report feelings of social disconnectedness in daily life. This study suggests that online interactions have real-world consequences for the emotional well-being of adolescents, but it is unclear if this relationship is limited to online peer interactions. Based on the results of studies reviewed in the introduction of this thesis, it is likely that both online and offline interactions with peers have similar consequences on the well-being of adolescents.

The other empirical article identified by this literature search involved exposing healthy males aged 18–23 years to a novel video game over a 10-day period, and then measuring their desire to play the game, as well as their neural reactions to stimuli depicting the game (D. H. Han et al., 2011). Participants who reported greater desire to play the video game showed greater activity in areas of the brain that have previously been found to be recruited when individuals with substance dependence were shown substance-related stimuli. However, the authors note that it's possible that the pattern of neural activity elicited by video game stimuli in these participants could reflect simply the emotional memory response to playing the game (D. H. Han et al., 2011). As the interpretation of the results of this paper relies on reverse inference (inferring cognition or mental states from brain activity patterns), it is not clear how this study contributes to our understanding of how Internet use could affect the adolescent brain.

| Title of Article | Authors | Category | Population | Methods | Relevance |
|---|---|---|---|---|---|
| Peer acceptance and rejection through the eyes of youth: pupillary, eyetracking and ecological data from the Chatroom Interact task | Silk JS, Stroud LR, Siegle GJ, Dahl RE, Lee KH, Nelson EE | Empirical | 9-17 years (n=60) | Pupillary and eyetracking analyses during simulated internet chatroom task | Experiment measured peer acceptance and rejection sensitivity in simulated Internet chatroom task |
| Brain activity and desire for Internet video game play | Han DH, Bolo N, Daniels MA, Arenella L, Lyoo IK, Renshaw PF | Empirical | 18-23 years (n=19) | MRI and fMRI measuring cue-induced activation to Internet video game stimuli after extensive game play | Experiment measured how the brain responds to Internet video game stimuli in healthy individuals |
| The digital revolution and adolescent brain evolution | Giedd JN | Review | Adolescence | Speculation on potential effects of the digital technologies on brain development | The essay topic is relevant, but relevant citations were lacking |
| Digital media, the developing brain and the interpretive plasticity of neuroplasticity | Choudhury S, McKinney KA | Review | Adolescence | Essay addressing common fears about the use and misuse of digital technologies on the adolescent brain | The essay topic is relevant, with relevant citations to empirical studies |

**Table 7.1**. Descriptions of studies classified as "empirical" or "review" articles from the literature search. Two studies were classified as empirical and two were classified as review articles. The article title, authors, category, population, methods, and relevance to the current literature review are described for each study.

**Table 7.2**. (part 1) Descriptions of studies classified as "clinical" articles from the literature search. Twenty studies were classified as clinical articles. The article title, authors, category, and population are described for 10 of the studies in this table.

| Title of Article | Authors | Category | Population |
|---|---|---|---|
| Voxel-level comparison of arterial spin-labeled perfusion magnetic resonance imaging in adolescents with internet gaming addiction | Feng Q, Chen X, Sun J, Zhou Y, Sun Y, Ding W, Zhang Y, Zhuang Z, Xu J, Du Y | Clinical | 15 adolescents with internet gaming addiction (IGA) & 18 matched controls |
| Altered default network resting-state functional connectivity in adolescents with Internet gaming addiction | Ding WN, Sun JH, Sun YW, Zhou Y, Li L, Xu JR, Du YS | Clinical | 17 adolescents with IGA & 24 control adolescents |
| Reduced orbitofrontal cortical thickness in male adolescents with internet addiction | Hong SB, Kim JW, Choi EJ, Kim HH, Suh JE, Kim CD, Klauser P, Whittle S, Yűcel M, Pantelis C, Yi SH | Clinical | 15 male adolescents with internet addiction disorder (IAD) & 15 male control participants |
| Gray matter and white matter abnormalities in online game addiction | Weng CB, Qian RB, Fu XM, Lin B, Han XP, Niu CS, Wang YH | Clinical | 17 adolescents with IGA & 17 matched controls |
| Decreased functional brain connectivity in adolescents with internet addiction | Hong SB, Zalesky A, Cocchi L, Fornito A, Choi EJ, Kim HH, Suh JE, Kim CD, Kim JW, Yi SH | Clinical | 22 adolescents with IAD & 11 controls |
| A voxel-based morphometric analysis of brain gray matter in online game addicts | Weng CB, Qian RB, Fu XM, Lin B, Ji XB, Niu CS, Wang YH | Clinical | 17 participants with OGA & 17 matched controls |
| Cortical thickness abnormalities in late adolescence with online gaming addiction | Yuan K, Cheng P, Dong T, Bi Y, Xing L, Yu D, Zhao L, Dong M, von Deneen KM, Liu Y, Qin W, Tian J | Clinical | 18 adolescents with OGA & 18 matched controls |
| Abnormal brain activation of adolescent internet addict in a ball-throwing animation task: possible neural correlates of disembodiment revealed by fMRI | Kim YR, Son JW, Lee SI, Shin CJ, Kim SK, Ju G, Choi WH, Oh JH, Lee S, Jo S, Ha TH | Clinical | 17 adolescents with IAD & 17 adolescent controls |
| Brain fMRI study of crave induced by cue pictures in online game addicts (male adolescents) | Sun Y, Ying H, Seetohul RM, Xuemei W, Ya Z, Qian L, Guoqing X, Ye S | Clinical | 10 males with addiction to specific online game & 10 matched controls |
| Reduced striatal dopamine transporters in people with internet addiction disorder | Hou H, Jia S, Hu S, Fan R, Sun W, Sun T, Zhang H | Clinical | 5 males with IAD & 9 matched controls |

| Title of Article | Authors | Category | Population |
|---|---|---|---|
| Abnormal white matter integrity in adolescents with internet addiction disorder: a tract-based spatial statistics study | Lin F, Zhou Y, Du Y, Qin L, Zhao Z, Xu J, Lei H | Clinical | 17 adolescents with IAD & 16 controls |
| Functional magnetic resonance imaging of brain of college students with internet addiction | Du W, Liu J, Gao X, Li L, Li W, Li X, Zhang Y, Zhou S | Clinical | 19 participants with OGA & 19 controls |
| Preliminary study of Internet addiction and cognitive function in adolescents based on IQ tests | Park MH, Park EJ, Choi J, Chai S, Lee JH, Lee C, Kim DJ | Clinical | 59 adolescents with IAD & 43 controls |
| Intervention on network craving and encephalofluctuogram in patients with internet addiction disorder: a randomized controlled trial | Zhu TM, Li H, Du YP, Zheng Z, Jin RJ | Clinical | 120 individuals with IAD |
| Microstructure abnormalities in adolescents with internet addiction disorder | Yuan K, Qin W, Wang G, Zeng F, Zhao L, Yang X, Liu P, Liu J, Sun J, von Deneen KM, Gong Q, Liu Y, Tian J | Clinical | 18 adolescents with IAD |
| Male Internet addicts show impaired executive control ability: evidence from a color-word Stroop task | Dong G, Zhou H, Zhao X | Clinical | 17 males with IAD & 17 gender-matched controls |
| Deficits in early-stage face perception in excessive internet users | He JB, Liu CJ, Guo YY, Zhao L | Clinical | 14 participants with IAD & 14 controls |
| Increased regional homogeneity in internet addiction disorder: a resting state functional magnetic resonance imaging study | Liu J, Gao XP, Osunde I, Li X, Zhou SK, Zheng HR, Li LJ | Clinical | 19 participants with IAD & 19 controls |
| Bupropion sustained release treatment decreases craving for video games and cue-induced brain activity in patients with Internet video game addiction | Han DH, Hwang JW, Renshaw PF | Clinical | 11 particiapnts with IGA & 8 controls |
| Gray matter abnormalities in Internet addiction: a voxel-based morphometry study | Zhou Y, Lin FC, Du YS, Qin LD, Zhao ZM, Xu JR, Lei H | Clinical | 18 adolescents with IAD & 15 matched controls |

**Table 7.2**. (part 2) Descriptions of studies classified as "clinical" articles from the literature search. Twenty studies were classified as clinical articles. The article title, authors, category, and population are described for 10 of the studies in this table.

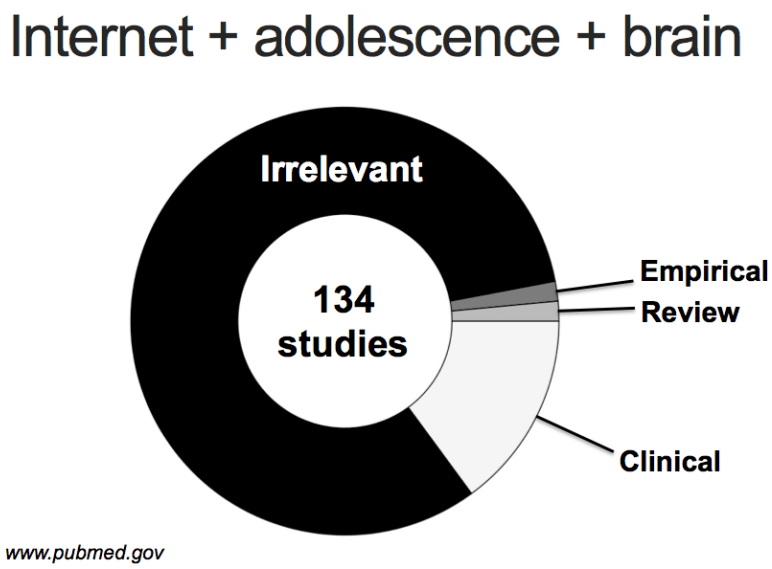


**Figure 7.1. Summary of pubmed literature search for Internet + adolescence + brain.** 134 studies were classified into four categories: Empirical, Clinical, Review, or Irrelevant.

## 7.4 Brain susceptibility

Just how much can we expect the adolescent brain to be affected by environmental influences like Internet use? Major brain changes, akin to what is suggested by the phrase 'rewiring the brain' are unlikely. Recent longitudinal brain-imaging studies have shown that major changes in brain structure and function might be largely related to genetic and trait differences between individuals.

Changes in brain structure, as measured by MRI, appear to be under strong genetic control during the transition between late childhood and early adolescence (van Soelen et al., 2012). Changes in the recruitment of the ventral striatum when receiving a reward across adolescence are predominantly related to individual differences in self-reported fun seeking (van Duijvenvoorde et al., 2014). These studies suggest that environmental influences, like Internet use, would have little effect on neural measures at this level. Well-established sensitive periods for

sensory processes and language acquisition end well before adolescence, but adolescence might encompass a sensitive period for sociocultural learning (reviewed in Chapter 1 and 8). If so, this would mean that adolescence is a time when we are honing our skills for navigating complex social interactions and that a lack of opportunities to engage in this skill-building behaviour could impede development. However, current evidence suggests that typical Internet activities do not impair social development during adolescence.

## 7.5 Internet use and adolescent health

Both adolescents and adults are now using the Internet more than ever. Evidence increasingly suggests that time spent online does not displace time spent doing other activities associated with health and well-being. Indeed, a recent longitudinal study of individuals aged 14–24 years (n=719) found a positive relationship between moderate Internet use and participation in 'real-world' activities such as sports and clubs (Romer, Bagdasarov, & More, 2013). Because the Internet can be used through various media such as mobile phones or computers Internet use sometimes falls under the category of 'screen based sedentary behaviour'. Although it is unclear how time spent specifically using the Internet relates to physical activity, a longitudinal study of individuals aged 11–13 years (n=908) suggests that engaging in screen-based sedentary behaviours such as computer use is not associated with less engagement in leisure-time physical activities (Gebremariam et al., 2013). Regarding social well-being, a review of the literature in 2009 supported the idea that communicating with friends through the Internet can increase adolescents' social connectedness (Valkenburg & Peter, 2009). These and other studies emphasise the need to distinguish between the effects of different Internet activities (e.g., information gathering, communication)

as well as specific aspects of Internet use that may be shared with other forms of media (e.g., screen time).

## 7.6 Internet use and cognition

At this time we cannot be sure whether Internet use is creating a generation with 'fundamentally different cognitive skills' (Purcell et al., 2012), although recent studies have begun to test the potential effects of widespread Internet use on the cognitive abilities of young adults. In 2011, Sparrow and colleagues tested how the expectation of having access to information at a later time affected the memory of undergraduate students (Sparrow, Liu, & Wegner, 2011). When expected to have future access to information, students were less likely to remember specific information but were more likely to remember where to find the specific information (Sparrow et al., 2011). A recent study tested how being part of highly connected networks (like the Internet) affected the propagation of correct information, as well as the underlying cognitive strategies needed to generate correct information, in a group of university students (Rahwan, Krasnoshtan, Shariff, & Bonnefon, 2014). The results of the study suggest that being part of highly connected networks can help individuals solve problems by facilitating the propagation of correct information, but that these networks do not propagate the cognitive strategies needed to obtain correct information on one's own (Rahwan et al., 2014). These cleverly designed experiments suggest that the effects of Internet use on cognition are likely nuanced, but could strengthen specific cognitive strategies in young adults.

## 7.7 Internet addiction

Although there are neuroimaging studies that have investigated the effects of Internet use on the adolescent brain, these studies have focused on adolescents classified as excessive Internet users (see Weinstein & Lejoyeux, 2013 for a review and Table 7.2). The results of these studies are unlikely to apply to the majority (an estimated 95.6%; see Durkee et al., 2012) of adolescents that do not qualify as excessive Internet users. What is not present in the current literature are studies that correlate brain measurements – along with behaviour, cognition, and well-being – with engagement in different Internet activities. This might not initially seem like a feasible method of experimentation, given the ever-increasing presence of the Internet in our lives. However, we can begin to address this question by utilising methods adopted in studies on the effects of other environmental influences (e.g., musical training) and by deconstructing Internet use into measurable components.

## 7.8 Learning from musical-training studies

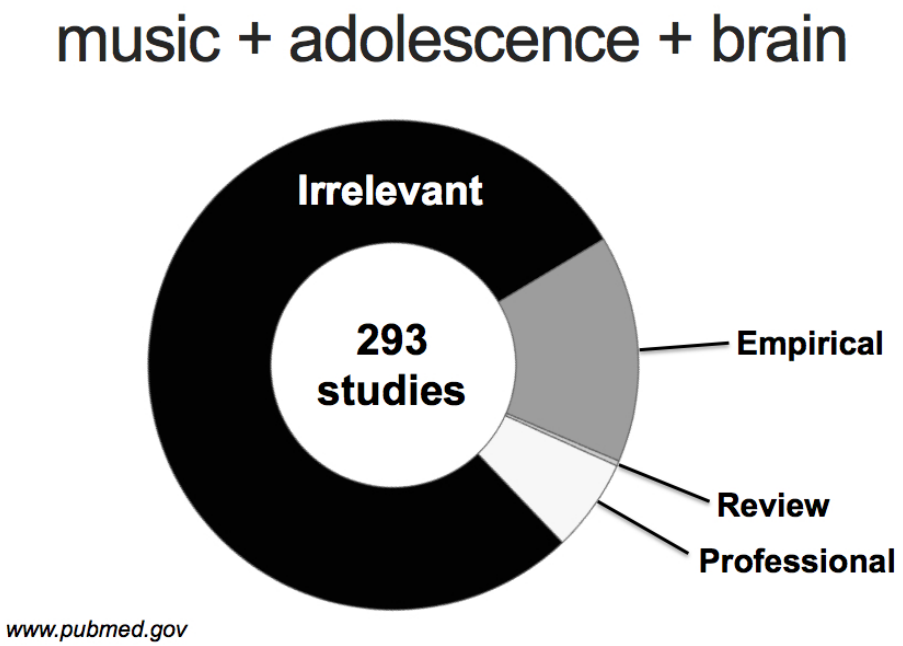


**Figure 7.2. Summary of pubmed literature search for music + adolescence + brain.** 293 studies were classified into four categories: Empirical, Professional, Review, or Irrelevant.

Like the few studies looking at the effects of Internet use on brain measures during adolescence, some studies of musical training compare the brains of the extreme end of the population (professional musicians) with the brains of non musicians (see Figure 7.2). However, some of these studies have adopted methods to measure how musical training in nonprofessionals relates to brain measures, behaviour, and cognition in both developing populations and adults (Bergman Nutley, Darki, & Klingberg, 2014; R. J. Ellis et al., 2012). These studies have largely adopted such methods to investigate whether there are particular developmental windows when musical training results in greater or fundamentally different effects. By collecting self-reported measures of the age at which participants began their musical training, as well as the duration and intensity of musical training, these studies are able to distinguish between training and maturational effects (Bergman Nutley et al., 2014; R. J. Ellis et al., 2012). It might be possible to adopt similar methods in future investigations of Internet use and its subcomponents. This could help clarify if aspects of Internet use during adolescence impact brain measures, behaviour, and cognition in a fundamentally different way from Internet use in adulthood.

## 7.9 Conclusion

In the 25 years since the World Wide Web was invented, our way of interacting with each other and our collective history has changed. Successfully navigating this new world is likely to require new skills, which will be reflected in our neural architecture on some level. However, there is currently no evidence to suggest that Internet use has had a profound effect on brain development. If we want to know how this highly connected world is impacting our brains, we will need to

conduct studies that investigate brain measures and their relationship to behaviour, cognition, and well-being in a representative sample of the population. These studies can draw from techniques adopted in studies of other environmental influences, such as musical training, and should differentiate between different Internet activities. Creative experimental designs have begun testing how certain aspects of Internet use can affect cognitive abilities, but many of these studies have been conducted only in adult samples. Finally, even if Internet use is impacting the developing brain during adolescence, we must not forget that the brains of adults remain capable of functional change. Indeed, Internet-based training programs are being developed to capitalise on just that (Bergquist et al., 2009).

# Chapter 8 Discussion

## 8.1 Summary of results

The work presented in this thesis demonstrates that adolescence is a period of substantial development in both in terms of social navigation and brain structure. The empirical studies conducted as part of this thesis provide support for the theory that adolescence is possibly a sensitive period to social signals in the environment, as both cognitive skills and regions of the brain involved in social development are undergoing significant changes between childhood and adulthood. Each of the studies conducted in this thesis is summarised below. I have expanded on the potential implications of each study and synthesised the results into the current adolescent literature. The limitations of these studies, and suggestions for future steps needed to address them, are also discussed in turn.

### 8.1.1 The development of intracranial volume

It is generally assumed that humans attain total intracranial capacity, or volume (ICV), by early adolescence (Courchesne et al., 2000; Pfefferbaum et al., 1994). This assumption has affected the way in which studies of structural brain development are conducted, with some researchers investigating the adolescent period opting to control for ICV or whole brain volume in their studies (Dennison et al., 2013; Østby et al., 2009; Urošević et al., 2012). It is thought that controlling for ICV will allow for better comparison between brain volumes, and eliminate the chance that differences in brain structure are due to individual differences in head size (Whitwell et al., 2001). However, it is unclear if this statistical procedure is advantageous for longitudinal investigations of brain development, where individual differences in brain structure are already accounted for by the

presence of two or more time points of data. Therefore, the study described in Chapter 3 used a longitudinal sample of individuals with at least three MRI scans between late childhood and early adulthood to examine: how ICV develops through the second decade, what physical processes are associated with ICV development, and how correcting for ICV could impact developmental studies.

The results of this study showed a protracted developmental pattern for ICV, with ICV increasing by ~12% between late childhood and early adulthood. This result suggests that human intracranial capacity (ICV) is still not fully mature by early adolescence, and that it could still be developing in some individuals through the teen years. However, the results of the second analysis conducted in Chapter 3 suggest that it might not possible to place a hard number on when ICV finishes developing, as its development is less related to age than it is to physical developmental factors. While ICV development was significantly related to a quadratic age model (see Figure 3.3), a quadratic height model was a significantly better fit, suggesting that changes in height are more related to changes in ICV than how long one has been alive. However, when all available measures of development and physical characteristics (age, pubertal stage, height, weight and gender) were considered in a multi-variable model of development, the best fitting model included height, pubertal stage, and gender. This result again suggests that physical developmental processes are related to ICV development more so than age. As individuals go through puberty and changes in height at different ages, it might be that we cannot adequately estimate an age in which ICV is mature. The final analysis conducted in Chapter 3 demonstrated that the method in which one controls for ICV impacts the perceived impact of gender on brain developmental trajectories. While gender still accounted for variance in an age model of grey

matter volume that included ICV as a covariate, gender did not account for variance in an age model of grey matter volume that had been corrected for ICV. This result implies that investigations that add ICV as a covariate to their models would assume that gender differences exist in brain developmental trajectories of cortical grey matter volume, whereas investigations that correct grey matter volume for ICV would assume that there were no gender differences in cortical grey matter volume development.

While the study conducted in Chapter 3 represents the first investigation of ICV development in a longitudinal sample, the results need to be replicated in different samples before methodological recommendations are made. To assist in this endeavour, the analysis code for this study has been made publicly available. Currently, this study is being replicated across three other longitudinal datasets of brain development in a collaboration effort across five different institutes/universities. Furthermore, as some researchers opt to control for whole brain volume rather than ICV (although, it should be noted, some studies cite early investigations of ICV correction methods (e.g., Sanfilipo et al., 2004) as their underlying impetus for controlling for whole brain volume (e.g., Dennison et al., 2013)), it would be beneficial if the same three analyses conducted in Chapter 3 were repeated for whole brain volume. A truly comprehensive study would address how controlling for ICV and/or whole brain volume affects the age trajectories and perceived gender influences of multiple brain volume measures. This is one of the aims of the multi-site collaboration project currently underway.

### 8.1.2 The developmental mismatch in structural brain maturation during adolescence

One of the most prevalent assumptions in developmental neuroscience is that subcortical regions of the brain involved in affect and reward processing are mature by adolescence, whereas prefrontal regions involved in cognitive control are still developing (Casey et al., 2008; Steinberg, 2008). This assumption underlies the popular theory that greater subcortical signaling, under-regulated by the prefrontal cortex, underlies typical adolescent risk-taking behaviours (Somerville et al., 2011). Therefore, it is thought that emotional contexts or impending rewards are more salient to adolescents relative to adults, when the mature prefrontal cortex is better able to modulate the subcortical signals. However, no study had directly assessed the relative development of these two systems within the same participants using a longitudinal design. Most support for this 'dual systems' hypothesis relied on cross-sectional data, and it is not known whether this pattern is present at an individual level. The study conducted in Chapter 4 used longitudinal structural MRI data to characterise the developmental trajectories of regions associated with risk-taking and sensation-seeking behaviours, namely, the amygdala, NAcc and prefrontal cortex PFC. Structural trajectories of grey matter volumes were analysed in 33 participants aged 7–30 years, each of whom had at least three high-quality MRI scans spanning three developmental periods: late childhood, adolescence and early adulthood. This study investigated two hypotheses proposed by the dual systems model: that subcortical regions involved in affect and reward (the amygdala and nucleus accumbens) mature before the prefrontal cortex; and that this developmental mismatch in maturity relates to risk-taking and sensation-seeking behaviours during adolescence.

On a group level, these results suggest that a mismatch in structural development exists between the amygdala and PFC during adolescence, but not necessarily between the NAcc and PFC, since these regions continue to show volume change into early adulthood. However, on an individual level, the results show wide variation in the presence or absence of a developmental mismatch between structures. At first, it seemed as though this individual variability could relate to individual differences in risk-taking and sensation-seeking behaviours. However, this study did not find a relationship between the level of self-reported risk-taking and sensation-seeking behaviours and the presence or absence of a developmental mismatch between the regions of interest. However, this study's failure to find a relationship between between brain structure and real-world behaviour could result from limitations associated with the study. Therefore, future studies are needed to unravel the nature of the relationship between brain development and behaviour in adolescence. Specifically, studies that measure brain maturity using metrics other than structural measures, such as functional connectivity (Dosenbach et al., 2010), should be used to assess patterns of brain development between the amygdala, NAcc and PFC.

### 8.1.3 Structural development of the social brain across adolescence

Social cognition provides humans with the necessary skills to understand and interact with one another. One aspect of social cognition, mentalising, is associated with a network of brain regions often referred to as the social brain, or mentalising brain network. This network consists of the medial prefrontal cortex [medial Brodmann Area 10 (mBA10)], temporoparietal junction (TPJ), posterior superior temporal sulcus (pSTS) and anterior temporal cortex (ATC). Although the functional development of the social brain has been studied extensively (see

Blakemore, 2008 for review), how these specific regions develop structurally across late childhood and adolescence had not been well established. The study described in Chapter 5 examined the structural developmental trajectories of social brain regions in the using longitudinal neuroimaging data from 288 participants (aged 7–30 years, 857 total scans). The developmental age trajectories of grey matter volume, cortical thickness and surface area were analysed using surface-based cortical reconstruction software and mixed modelling.

The results of the analysis in Chapter 5 found evidence for continued development of social brain regions across adolescence. Grey matter volume and cortical thickness in mBA10, TPJ and pSTS decreased from childhood into the early twenties. The ATC increased in grey matter volume until adolescence and in cortical thickness until early adulthood. Surface area for each region followed a cubic trajectory, reaching maximum values in early or pre-adolescence before decreasing into the early twenties. Sex differences were observed in grey matter volume and surface area, but not in cortical thickness, for all regions of interest, with males displaying greater grey matter volumes and surface areas than females.

This study was the first to investigate structural changes in regions of the social brain network across development using a large, longitudinal sample. The results show that regions of the human brain associated with the ability to infer the intentions, beliefs and desires of others are continuing to develop structurally across adolescence. This prolonged development supports the idea of adolescence as a sensitive period for neural changes in areas of the brain involved in mentalising, or attributing mental states to others. Adolescence is a time of

physical and mental transition marked by the onset of puberty. At the same time, there are changes in the social environment that adolescents have to successfully navigate, which involves recruiting their mentalising skills. Continued development in the structure of the brain may contribute to the flexibility necessary for this transition.

### 8.1.4 Multitasking during social interactions in adolescence and early adulthood

Building on the knowledge obtained in the previous chapters, which provided evidence for adolescence as a time of continued development of complex social cognitive skills, the study in Chapter 6 investigated the interplay of executive functioning and perspective taking during complex social interactions. Within the typical social environment, we are regularly faced with situations that require multitasking whilst engaging in a social interaction. For example, we often multitask during social interactions by simultaneously keeping track of other, non-social information. Therefore, it is important to understand how simultaneously keeping in mind extraneous information influences our ability to engage in a communicative task with another person. In the study described in Chapter 6, I investigated keeping track of non-social information impacts the ability to navigate social interactions in both adolescents and adults, as the ability to navigate social interactions continues to develop throughout human adolescence. Participants aged 11–17 and 22–30 years old were instructed to carry out two tasks, one social and one non-social, within each trial. The social task involved referential communication, requiring participants to use social cues to guide their decisions, which sometimes required taking a different perspective. The non-social task manipulated cognitive load by requiring participants to remember non-

social information in the form of one two-digit number (low load) or three two-digit numbers (high load) presented before each social task stimulus.

Overall, adolescents were less adept at multitasking than adults when under high cognitive load. Importantly, these results suggest that processing and using social cues to guide behaviour is relatively automatic when the partner in a social interaction shares the same perspective. Both adult and adolescent participants were, on average, faster and more accurate when using social cues to guide decisions. However, multitasking accuracy was impaired when participants had to inhibit their own egocentric perspective. These results suggest that multitasking during social interactions incurs performance deficits, and that adolescents, compared to adults, are more sensitive to the effects of cognitive load while multitasking.

This study contributes to the understanding of the limits of human performance in social interactions, and that the ability to multitask is still developing between adolescence and adulthood. As adolescence is a time when complex social cognitive skills are changing along with the social environment (reviewed in Chapter 1), this study examined how cognitive control abilities, such as the ability to manipulate information in WM, influence the continued development of social navigation skills between adolescence and adulthood. The results of this study have potential real-world implications. For example, the results suggest that the natural pace of social interactions, such as everyday conversations, could be disrupted when adolescents or adults are simultaneously keeping track of extraneous information. However, as adolescents appear to be more affected cognitive load than adults are in multitasking scenarios, multitasking activities

that might not seem cognitively taxing for adults could prove more difficult for some adolescents. For example, in-class group work might be particularly difficult for adolescents who are already struggling with the assignment topic. Future studies that use more ecologically valid task scenarios (such as virtual reality) are needed to further explore what factors in multitasking scenarios most influence performance. In addition, it is not known if the ability to successfully multitask in social interactions could be improved through training or by manipulating factors in the environment. Finally, to further understand how brain development could be related to the development of multitasking abilities, neuroimaging studies are needed to explore how cognitive control networks are involved in multitasking scenarios in both adolescents and adults.

## 8.2 Wider implications

### 8.2.1 Is the human brain particularly sensitive to social signals during adolescence?

My review of the literature in Chapter 1 outlined evidence from the psychology and neuroscience literatures to support the view of adolescence as a period particularly sensitive to social environmental cues. However, two further lines of evidence need to be acquired to the theory that adolescence is a *sensitive period* of social development: a) the brain during adolescence (more than in childhood and adulthood) is particularly susceptible to social environmental cues; and b) changes in the brain during adolescence reflect particular susceptibility to social environmental cues (more than other types of stimuli). That is, is the human brain organised in such a manner that reflects our ancestors navigating increasingly complex social environments, or foraging in increasingly unstable climates? Similarly, is the protracted development of the mentalising brain network

reflective of the need for later acculturation into one's society and culture? Acculturation, or adaptation to the mainstream culture of where one has immigrated, occurs more rapidly at younger ages (1 to 15 years) (Cheung, Chudek, & Heine, 2011), suggesting that the sensitive period for cultural learning is not adolescent-specific but instead that cultural sensitivity may begin to close during adolescence. Perhaps the cognitive and behavioural abilities that emerge during adolescence enhance social signals or allow them to be more easily integrated.

### 8.2.2 Mental Health

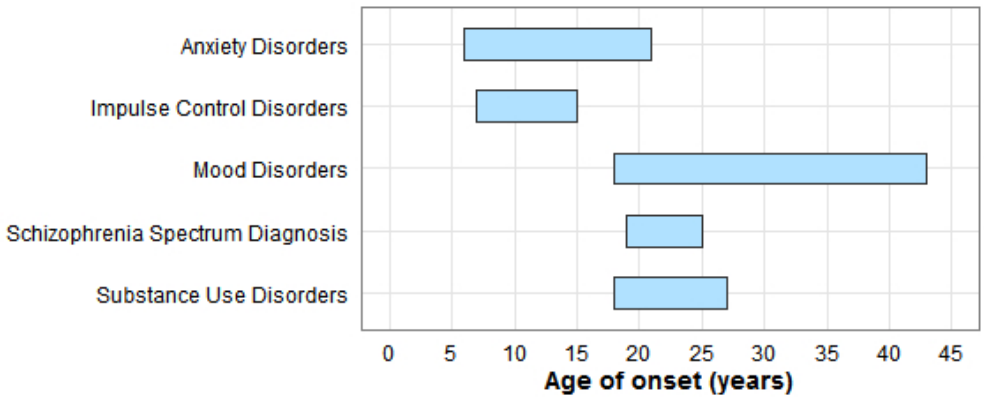


**Figure 8.1. Ranges of onset age for common psychiatric disorders.** The graph is based on the results of a nationally representative epidemiological survey of mental disorders and demonstrates that most individuals diagnosed with a mental disorder show the beginnings of the illness in late childhood or in adolescence. Adapted from Fuhrman et al. (under review); data from Kessler et al. (2005; 2007).

Mental health disorders often have an onset in adolescence (Kessler et al., 2005, 2007; Kessler & Wang, 2008) (Figure 8.1). The heightened vulnerability to psychiatric conditions during adolescence has been proposed to relate to genetically preprogrammed neural development at the same time as new stresses and challenges emerge in the environment (Andersen & Teicher, 2008; Leussis & Andersen, 2008). Stress exposure, including social stress, during adolescence may

be longer lasting and qualitatively different from stress exposure at other periods of life, possibly due to the interaction between the developing hypothalamic-pituitary-adrenal (HPA) axis and glucocorticoids (for review, see McCormick, Mathews, Thomas, & Waters, 2010). This work provides strong evidence for adolescence as a sensitive period for social signals. One reason why adolescents show increased sensitivity to stress-induced levels of glucocorticoids is the increase in glucocorticoid regulation in the human prefrontal cortex (Perlman, Webster, Herman, Kleinman, & Weickert, 2007). This neural change, which increases from infancy through childhood and adolescence, might make adolescents more vulnerable to psychiatric illnesses (Perlman et al., 2007).

### 8.2.3 Educational implications

Adolescence represents a period of brain development during which environmental experiences do profoundly shape the developing brain. If early childhood is seen as a major opportunity for teaching, so too might adolescence. It is only recently that teenagers have been routinely educated in the West. In many countries a large proportion of teenagers have no access to secondary school education. And yet the adolescent brain is malleable and adaptable, which makes this time of life an excellent opportunity for learning and creativity. Risk taking in an educational context is a vital skill that enables progress and creativity. Although some adolescents use risk taking to achieve great things, many are worried about taking risks in the context of learning. The heightened risk taking in this age group should be harnessed for learning and creativity.

A prevailing view in adolescent research is that certain behaviours are desirable (e.g., long-term planning), and certain behaviours are undesirable (e.g., risk

taking). Although long-term planning can help many individuals attain high quality and stable adult lives, other external factors may prevent individuals from attaining this goal despite their using long-term planning (B. J. Ellis et al., 2012). In certain situations, taking a risk might actually be more likely to give the individual a chance to obtain the preferred outcome. The research described in this thesis emphasises the role of contextual cues in influencing adolescent behaviours. A shift from treating adolescent behaviours, especially risk-taking behaviours, in isolation to a model that integrates social environmental cues might enhance our understanding of adolescent behaviours and improve interventions. What is sometimes seen as the problem with adolescents – risk taking, poor impulse control, self-consciousness, and so forth – is actually reflective of brain changes that provide an excellent opportunity for education and social development.

Adolescence is a time of opportunity for learning new skills and forging an adult identity. Research on brain development suggests that adolescence might represent a period of relatively high neural plasticity, in particular in brain regions involved in executive function and social cognition. The research on the brain basis of social development in adolescence might have implications for "when to teach what" and could inform both curriculum design and teaching practice with the aim of ensuring that classroom activities exploit periods of neural plasticity that facilitate maximal learning.

### 8.2.4 Legal implications

Developmental neuroscience has already affected legal proceedings in United States by calling into question the sentencing procedures applied to adolescents

(see Steinberg, 2013), and many developmental scientists are still struggling with questions of culpability during an age of relative brain immaturity (Cauffman & Steinberg, 2000; Steinberg, 2009; Steinberg & Scott, 2003). Although the discussion on culpability and the brain is ongoing, evidence from multiple fields supports the need for special consideration in prosecuting and punishing adolescents. Twenty years ago, Terrie Moffitt presented evidence supporting the idea that the majority of adolescents who engage in criminal behaviour will do so during adolescence and at no other period of their life (Moffitt, 1993). Such problem behaviours have also been shown to decrease without formal training (Chamberlain & Moore 1998). Further, interventions that segregate adolescents engaging in problem behaviours into groups can actually be harmful (Dishion, Ha, & Véronneau, 2012; Dishion & Tipsord, 2011; B. J. Ellis et al., 2012). The social augmentation hypothesis suggests that peer exclusion in adolescence can lead to neuroanatomical shifts in reward sensitivity, therefore making the adolescent more susceptible to peer influence (Dishion et al., 2012). The research reviewed in this thesis would support this speculative hypothesis, and future work will need to integrate measures of social exclusion and peer influence with neuroimaging paradigms, as some have already begun to do (Peake, Dishion, Stormshak, Moore, & Pfeifer, 2013).

Psychology and intervention research provide a strong argument for reducing situations in which high-risk behaviours such as gang affiliation and crime are rewarded through positive peer responses (Dishion & Tipsord, 2011). The capacity for change is reflected in the extended neuroanatomical and functional development of the human brain. By understanding and harnessing the plasticity of the brain during adolescence, legal interventions might better prevent

reoffending and promote prosocial behaviour. It is important that these interventions take into account not only the adolescent but also the influences of the social and physical environments in which the adolescent finds him or herself. Evidence from neuroscience and psychology studies shows that the social environment during adolescence has a profound impact on life course trajectories, and it is necessary to attempt to change the adolescent engaging in criminal behaviours as well as the social environment that may promote such behaviours.

### 8.2.5 Social implications

A consequence of research on adolescence might be a change in how adolescents are perceived, including how adolescents perceive themselves, the period of adolescence and what can be expected, and how adolescents interpret their experiences in the world. Research on adolescent brains and behaviours has penetrated multiple media outlets and is a perennial topic that receives much attention. One study has investigated how adolescents understand and feel about research on the adolescent brain (Choudhury, McKinney, & Merten, 2012). The participating adolescents in this study felt that although research on the adolescent brain is necessary and important, the model of the adolescent brain as an explanation for adolescent behaviour is insufficient (Choudhury et al., 2012). Interestingly, participants were less interested in how neuroscience could influence how they understand themselves and more interested in how research on the adolescent brain could influence the perspectives of adults (Choudhury et al., 2012). They pointed out the potential for neuroscience research to perpetuate stereotypes or combat stereotypes, depending on how adults incorporate research in their understanding of adolescence (Choudhury et al., 2012).

Adolescents are sensitive to the signals within their social environment, and these signals can impact how likely they are to invest in the future. A recent report suggested that adolescents perceive their risk of dying soon as higher than it actually is (Fischhoff, Bruine de Bruin, Parker, Millstein, & Halpern-Felsher, 2010). This perception may impact the likelihood of engaging in behaviours reflecting a faster life history strategy, although this has not been directly tested. Indeed, the authors voice similar concerns in the first sentence of the report: "Adolescents' willingness to prepare for the future depends, in part, on their confidence in living long enough to get a return on that investment" (Fischhoff et al., 2010). Perceived threats and crime expectations in the environment, but not actual experience with violence, correlated with mortality judgments (Fischhoff et al., 2010). Larger social structures have consequences for the health of adolescents, with factors such as inequality and poverty reducing adolescent health (Viner et al., 2012).

## 8.3 Outstanding issues and future directions

While much progress has been made in our understanding of social cognitive and brain development during adolescence, many questions remain unanswered. The following sections highlight three directions that I feel would substantially improve the field of adolescent development.

### 8.3.1 Relating risk taking in the lab to real world outcomes

It is unclear just how much risk-taking behaviour is influenced by neurotypical brain development. Indeed, the popular theory addressed in Chapter 4, which assumes that neurotypical differences in brain development underlie the risk-taking behaviours observed during adolescence, has been increasingly called into

question over the past few years (Bjork & Pardini, 2015; Crone & Dahl, 2012; Duijvenvoorde et al., 2015; Pfeifer & Allen, 2012). It is likely that the more nuanced models proposed in these recent reports will be better able to account for individual differences in risk-taking behaviour during adolescence. However, the practical relevance of these models remains unexplored. For example, some neuroscientists argue that the adolescent peak in arrest rates can be explained by neurotypical development (Cohen & Casey, 2014). However, the arrest rates for juveniles in the United States has declined 54% between 1996 and 2011 (Office of Juvenile Justice and Delinquency Prevention, 2014), but this decrease is not likely due to changes in how the human brain develops. Furthermore, it is commonly assumed that risk-taking behaviour in adolescence accounts for a large increase in morbidity and mortality rates. The underlying assumption is that addressing preventable adolescent risk-taking behaviours, such as substance abuse, unsafe sexual practices, and dangerous driving, will decrease the morbidity and mortality rates of this age period. However, public health reports do not provide information about the riskiness of the behaviours individuals were engaged in at the time of injury/death. For example, the leading cause of death for 10–20 year olds is 'unintentional injury' – more specifically 'unintentional motor vehicle traffic', and the leading cause of injury for 10–20 year olds is 'unintentional struck by/against' (Kann et al., 2014). Perhaps research on adolescent driving behaviours could glean more insight as to the precedent behaviour of real world maladaptive outcomes (Olsen, Shults, & Eaton, 2013; Simons-Morton, Lerner, & Singer, 2005). Such investigations have found that behaviours other than risk taking could be the link between motor vehicle injuries/fatalities and adolescent behaviour, such as distraction (Klauer et al., 2014), or cognitive load (Pradhan et al., 2014). It is even possible that adolescents are harmed in motor vehicle

accidents through other means (e.g., as a passenger or a pedestrian). However, these alternative explanations remain underexplored compared to the popular notion that adolescents' active engagement in risk-taking behaviour underlies their highest driver of mortality and morbidity – accidents.

### 8.3.2 Development of internalised models of social agents

The aim of several studies in both this thesis and the developmental cognitive literature involve understanding how adolescents develop the ability to understand other people. However, most of what we know about how individuals understand other people is based on explicit measures of theory of mind. Following a brief review of the current literature, described below, I feel that future investigations in which more subtle measures of social cognition – such as the capacity to create, manipulate and apply internal models of other agents – are warranted.

The capacities needed to represent internal models of social agents develop early. By their first birthday, infants are not only able to associate mental attributes to specific agents (Buresh & Woodward, 2007), but they can also track the identities of individual social actors (Xu & Carey, 1996). There is less research on how young children map the characteristics of specific social actors onto internal models. Some evidence suggests that young children use their knowledge about the spatiotemporal history of specific agents in order to determine identity (Gutheil, Gelman, Klein, Michos, & Kelaita, 2008). And between the ages 5–6 years and 9–10 years, children begin to use trait inferences more consistently to predict the behaviours of others (Alvarez, Ruble, & Bolger, 2001).

The prevalence of imaginary companions in childhood provides some support that the ability to create and reason with internal models of specific agents comes online early in development. In a large sample of children between ages 5–12 years, approximately half reported having interacted with imaginary companions (Pearson et al., 2001). When interviewed, mothers most frequently report the "need for a relationship" as the reason why their child has created an imaginary companion, and indeed first born or only children are more likely to have imaginary companions (Gleason, Sebanc, & Hartup, 2000). Evidence suggests that children are able to integrate physical characteristics and personality into their models of imaginary companions, and the majority of children have conversations with their imaginary companions (Gleason et al., 2000).

However, as discussed throughout this thesis, the social world becomes more complex after the onset of puberty. The main theory addressed in this thesis suggests that the period of adolescence is a time when we hone many of the skills necessary to navigate the social environment. The ability to understand the mental states of others, termed mentalising, is one such skill. Understanding the beliefs, desires and intentions of others not only allows us to better predict the actions of others, but also understand what others think of us (Pfeifer & Peake, 2012). The opinions of peers become increasingly important in adolescence, and social exclusion can affect mood more profoundly in this period of life than in adulthood (Sebastian et al., 2010; reviewed in Chapter 1). However, it's clear that the identity of the peer matters, and adolescents value the perceptions of specific individuals based on a number of factors. Unlike children, adolescents can accurately perceive their rank within a social hierarchy (Savin-Williams, 1979), and the transition into adolescence is often marked by an increasing desire for

consensual popularity (Eder, 1985). To manoeuvre within these complex social systems, adolescents must be able to not only use generic sociocognitive skills such as mentalising, but track, update and predict the behaviours of specific individuals involved in everyday 'dramas' (Marwick & boyd, 2011). Increasing evidence suggests that adolescents monitor previous social interactions and modulate their behaviour with different peers to promote social stability and fairness (Güroğlu, van den Bos, & Crone, 2014; Will, Crone, van den Bos, & Güroğlu, 2013), and that this ability continues to develop between early and late adolescence.

While many social neuroscience studies have focused on the ability to process the mental states of a generic other, increasing evidence suggests that we process specific individuals differently. For example, adolescents recruit the mentalising brain network more when processing the outcomes of a gambling task when the earnings were going to another individual versus to the participant (Braams, Peters, Peper, Güroğlu, & Crone, 2014). However, activity in the ventral striatum was modulated based on the recipient of the reward, with greater activity observed following gains than losses for oneself and friends, whereas the opposite pattern was observed for antagonists (Braams et al., 2014). Similarly, when asked to reflect on their own personality traits from the perspective of their mother or best friend, adolescents recruited the mentalising brain network in a context-dependent manner (Pfeifer et al., 2009). Areas of the mentalising brain network were more active when adolescents were asked to infer how their mother might judge their academic abilities, and when asked to infer how their best friend might judge their social abilities (Pfeifer et al., 2009). These results add to a long history of psychological evidence that the development of identity in adolescence is partly

built on the perspectives of others (Pfeifer & Peake, 2012; Sebastian et al., 2008), but they also suggest that tracking and modelling the perspectives of specific individuals is a necessary ability for navigating this developmental challenge.

Studies using multi-round games that require participants to learn the trustworthiness of another player show that adolescents and adults are similarly able to quickly update internal models of specific agents on this dimension, but may use different cognitive strategies to do so (Fett, Gromann, Giampietro, Shergill, & Krabbendam, 2013). Future work is needed to understand what cognitive capacities related to creating, maintaining, and reasoning with internalised models of social agents are still developing throughout adolescence. It is also unclear how much individuals differ in their ability to update models of specific agents in response to socially relevant information.

### 8.3.3 Making science open to all

In 2010, the first scientific paper written by school children (8-10 years old) was published in Biology Letters (Blackawton et al., 2011). It was on the foraging strategies of bees, and began with the phrase "Once upon a time". What struck me when I read this study was not the kid-friendly language – although it is one of the most enthralling scientific papers I've ever read – but the unorthodox perspectives embedded within the study. The study's novel perspectives should not be surprising, given that children are typically not tied down by the same assumptions as adults who have spent decades within scientific institutions. It made me wonder what possible insights and discoveries are lost when only traditional scientists are conducting science.

In the past years, 'citizen science' has gained traction in the media, and big data projects harnessing the power of human data processing capabilities are increasing visible (e.g., Galaxy Zoo, Eyewire). While these projects are a major step toward making science more accessible to those outside traditional academic or institutional settings, they limit citizens to the roles of data collector or processor. I propose that we need more informal or "amateur" scientists asking the questions, designing the studies, and interpreting the answers.

Every year the Intel International Science and Engineering Fair features scientific research conducted by teenagers. In 2012, Jack Andraka won the fair's grand prize for his discovery of an elegant and inexpensive method for the early detection of cancer. But Andraka had to overcome several obstacles to do so. First, as a high school student with no formal institutional ties, he was unable to read any scientific literature locked behind paywalls. And even after he formulated his hypothesis, he was rejected from 199 researchers that he'd applied to work with in order to test it.

Barriers inhibiting scientists doing research outside of traditional settings need to be broken. All individuals should have access to the knowledge gathered from scientific research. More and more scientists are choosing to publish their work in journals that do not require readers to pay excessive fees or to be members of institutions that do so on their behalf. Many scientists bypass this barrier altogether and share their work freely outside of journals. Some even go further and share their data, experiments, and analysis methods. Openly sharing science not only allows untraditional scientists access to the same resources as scientists

tied to institutions, but provides the transparency needed to conduct replications, detect potential errors, and move the field forward.

However, the infrastructure to conduct science outside of traditional institutional settings has far to go. At times, getting approval to do your research takes longer than the rest of the process combined. David Lang, co-founder of OpenROV, recently wrote about the obstacles he encountered when trying to bring a group of amateur ocean explorers to the Sea of Cortez. Even after the group had overcome one frequent obstacle facing amateur scientists – building low-cost tools to conduct the research (in this case, underwater robots) – they were unable to obtain the permits to collect samples because they were not connected to an institution. Undoubtedly, the regulations and ethical checks imposed by research institutions are necessary to ensure no damage is done to the planet or the creatures that inhabit it, but perhaps they can become unbound from traditional institutional settings.

Doing science does not require the ability to flourish in an academic or institutional environment. Nor does it require years of specialised training. Yet, many barriers exist to those who do not possess these non-scientific qualifications. We need to accommodate those conducting research outside of traditional settings. This means creating the necessary infrastructure, and pushing ourselves to go beyond traditional examples of citizen science, where the citizens act as data-processors, to include non-traditional scientists in other aspects of the scientific process such as experimental design and data interpretation. This will bring much needed diversity into science, from which we will all benefit.

## 8.4 Overall summary

This thesis investigated the development of social interactions and relevant brain networks during the period of adolescence, to present new evidence for the theory that adolescence is a sensitive period for social cognitive development. While the results presented in this thesis share new insights, and challenge predominant theories, on brain development and social cognition during adolescence, future research is needed. Specifically, future studies should a) concurrently measure structural brain development and behaviour; b) measure the internalisation of social models during development; c) incorporate the perspectives of adolescents into research design and interpretation to create more ecologically-valid tasks; and d) directly assess how behaviours observed during laboratory tasks (such as risk taking) relate to public health outcomes.

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Appendix 2.1

Dear Participant,

As part of our ongoing study of typical brain development, we are interested in relating brain development to behaviors, thoughts, and feelings that our participants had when they were teenagers. We have attached to this sheet a number of questionnaires asking you to reflect on behaviors you may have engaged in or thoughts and feelings you may have had when you were a teenager, around when you were between 13 and 18 years old. It may be hard to remember, but we do ask that you try to be as honest as possible when answering these questions. We realize that some of the questions relate to particularly sensitive information, but be assured that, as always, your answers are strictly confidential. You can skip any question that you are uncomfortable answering. We appreciate your ongoing participation in this brain imaging study, and thank you for your contribution to science!

Sincerely,

The Child Psychiatry Branch
National Institute of Mental Health

The next 3 questions ask about you as a teenager. Please circle your responses and fill in the box. For the present purposes, risky behavior is defined as behavior that is unsafe or might result in negative consequences.

1. How old were you when you engaged in the most *risky* behavior?
   A. 13
   B. 14
   C. 15
   D. 16
   E. 17
   F. 18
   G. I don't think I engaged in risky behavior during this time.

2. Compared to your peers, how much risky behavior did you engage in as a teenager?
   A. Much more than my peers
   B. More than my peers
   C. About the same as my peers
   D. Less than my peers
   E. Much less than my peers

3. Please describe the types of risky behaviors you engaged in as a teenager.

Directions: Please read the following statements and circle whether you feel the statement was true or false for you when you were a teenager.

**When I was a teenager…**

1. I liked to have new and exciting experiences and sensations even if they were a little frightening.
    A. True
    B. False

2. I liked doing things just for the thrill.
    A. True
    B. False

3. I liked to do things that were a little frightening.
    A. True
    B. False

4. I would try anything once.
    A. True
    B. False

5. I did ‘crazy’ things just for fun.
    A. True
    B. False

6. I liked wild and uninhibited parties.
    A. True
    B. False

| Directions: On a scale of 1 (never) to 7 (very often), how often did you engage in each of these activities when you were a teenager? | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **Never** | | | | | | **Very Often** |
| 1. | Missed class or work | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 2. | Smoked marijuana | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 3. | Disturbed the peace | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 4. | Left a social event with someone I had just met | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 5. | Drank alcohol too quickly | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 6. | Tried/used drugs other than alcohol or marijuana | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 7. | Drank more than 5 alcoholic beverages | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 8. | Grabbed, pushed, or shoved someone | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 9. | Drove after drinking alcohol | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 10. | Not studied for exam or quiz | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 11. | Damaged/destroyed public property | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 12. | Had sex without protection against pregnancy | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 13. | Left tasks or assignments for the last minute | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 14. | Hit someone with a weapon or object | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 15. | Rock or mountain climbed | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 16. | Had sex without protection against sexually transmitted diseases | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 17. | Played contact team sports | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 18. | Failed to do assignments | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 19. | Slapped someone | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 20. | Did not study or work hard enough | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 21. | Punched or hit someone with fist | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 22. | Made a scene in public | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 23. | Had sex with multiple partners | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 24. | Snow or water skied | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 25. | Mixed drugs and alcohol | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 26. | Got into a fight or argument | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 27. | Played individual sports | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 28. | Played drinking games | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 29. | Had sex with someone I had just met or didn't know well | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 30. | Carried a weapon | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

**PAST FREQUENCY**

For each of the activities listed below, please indicate how many times you participated in this activity **during the year that you were most risky as a teenager.**

| | | **Within 1 year** |
|---|---|---|
| 1. | Missed class or work | _____ |
| 2. | Smoked marijuana | _____ |
| 3. | Disturbed the peace | _____ |
| 4. | Left a social event with someone I had just met | _____ |
| 5. | Drank alcohol too quickly | _____ |
| 6. | Tried/used drugs other than alcohol or marijuana | _____ |
| 7. | Drank more than 5 alcoholic beverages | _____ |
| 8. | Did not study for an exam or quiz | _____ |
| 9. | Drove after drinking alcohol | _____ |
| 10. | Grabbed, pushed, or shoved someone | _____ |
| 11. | Damaged/destroyed public property | _____ |
| 12. | Sex without protection against pregnancy | _____ |
| 13. | Left tasks or assignments until the last minute | _____ |
| 14. | Hit someone with a weapon or object | _____ |
| 15. | Rock or mountain climbed | _____ |
| 16. | Had sex without protection against sexually transmitted diseases | _____ |
| 17. | Played contact team sports | _____ |
| 18. | Failed to do assignments | _____ |
| 19. | Slapped someone | _____ |
| 20. | Did not study or work hard enough | _____ |
| 21. | Punched or hit someone with fist | _____ |
| 22. | Made a scene in public | _____ |
| 23. | Snow or water skied | _____ |
| 24. | Mixed drugs and alcohol | _____ |
| 25. | Got into a fight or argument | _____ |
| 26. | Played individual sports | _____ |
| 27. | Played drinking games | _____ |
| 28. | Sex with someone I had just met or didn't know well | _____ |
| 29. | Carried a weapon | _____ |

The next 5 questions ask about safety precautions you may have taken **when you were a teenager**.

1. When you rode a bicycle, how often did you wear a helmet?
   A. Always wore a helmet
   B. Most of the time wore a helmet
   C. Sometimes wore a helmet
   D. Rarely wore a helmet
   E. Never wore a helmet
   F. I did not ride a bicycle when I was a teenager

2. How often did you wear a seat belt when riding in a car driven by someone else?
   A. Always
   B. Most of the time
   C. Sometimes
   D. Rarely
   E. Never

3. How often did you ride in a car or other vehicle driven by someone who had been drinking alcohol?
   A. Daily
   B. 3-4 times/week
   C. 1-2 times/week
   D. Once per month
   E. Rarely
   F. Never

4. How often did you drive a car or other vehicle when you had been drinking alcohol?
   A. Daily
   B. 3-4 times/week
   C. 1-2 times/week
   D. Once per month
   E. Rarely
   F. I didn't drive a car after drinking alcohol as a teenager
   G. I didn't drive a car when I was a teenager

5. How often did you drive over 90 mph?
   A. Daily
   B. 3-4 times/week
   C. 1-2 times/week
   D. Once per month
   E. Rarely
   F. I didn't drive over 90 mph as a teenager
   G. I didn't drive a car when I was a teenager

The next 7 questions ask about your substance use **when you were a teenager**. Please circle the correct response.

| **How old were you when you engaged in the following activities for the first time?** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Never | 8 years or younger | 9 or 10 years | 11 or 12 years | 13 or 14 years | 15 or 16 years | 17 years or older |
| 6. | Smoked a whole cigarette? | A | B | C | D | E | F | G |
| 7. | Smoked marijuana? | A | B | C | D | E | F | G |
| 8. | Had your first drink of alcohol other than a few sips? | A | B | C | D | E | F | G |
| 9. | Tried/used drugs other than alcohol or marijuana? | A | B | C | D | E | F | G |

10. How often did you smoke cigarettes?
    A. Daily
    B. 3-4 times/week
    C. 1-2 times/week
    D. Once per month
    E. Rarely
    F. I didn't smoke cigarettes as a teenager

11. How often did you have 5 or more drinks of alcohol in a row, that is, within a couple of hours?
    A. Daily
    B. 3-4 times/week
    C. 1-2 times/week
    D. Once per month
    E. Rarely
    F. I didn't have 5 or more alcoholic drinks in a row as a teenager

12. How often did you did you use an illicit drug or prescription drug that you didn't have a prescription for?
    A. Daily
    B. 3-4 times/week
    C. 1-2 times/week
    D. Once per month
    E. Rarely
    F. I didn't use any illicit drugs as a teenager

The next 6 questions ask about your sexual behavior **when you were a teenager**.

13. How old were you when you had sexual intercourse for the first time?
    A. 12 years or younger
    B. 13 years
    C. 14 years
    D. 15 years
    E. 16 years
    F. 17 years
    G. 18 years or older
    H. I have never had sexual intercourse

14. Within a given **year,** on average, with how many people did you have sexual intercourse?
    A. 1 person
    B. 2 people
    C. 3 people
    D. 4 people
    E. 5 people
    F. 6 or more people
    G. I have never had sexual intercourse

15. Did you and your partner(s) use a condom when you had sexual intercourse?
    A. Always
    B. Most of the time
    C. Sometimes
    D. Rarely
    E. Never
    F. I have never had sexual intercourse

16. When you were a teenager, what method did you and your partner(s) most regularly use to prevent pregnancy? (Select only one response.)
    A. I have never had sexual intercourse
    B. No method was used to prevent pregnancy
    C. Birth control pills
    D. Condoms
    E. Depo-Provera (or any injectable birth control), Nuva Ring (or any birth control ring), Implanon (or any implant), or any IUD
    F. Withdrawal
    G. Some other method
    H. Not sure

17. What is your current level of education?

    _____

18. What is your current annual income?

    _____

Directions: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you acted and thought when you were a teenager. **Please answer each of the questions referring to what you were like as a teenager.** Read each statement circle the appropriate number on the right side of this page. Do not spend too much time on any statement.

**When I was a teenager…**

| | | Rarely/ Never | Occa- sionally | Often | Usually/ Always |
|---|---|---|---|---|---|
| 1. | I planned tasks carefully. | 1 | 2 | 3 | 4 |
| 2. | I did things without thinking. | 1 | 2 | 3 | 4 |
| 3. | I made up my mind quickly. | 1 | 2 | 3 | 4 |
| 4. | I was happy-go-lucky. | 1 | 2 | 3 | 4 |
| 5. | I didn't "pay attention." | 1 | 2 | 3 | 4 |
| 6. | I had "racing" thoughts. | 1 | 2 | 3 | 4 |
| 7. | I planned trips well ahead of time. | 1 | 2 | 3 | 4 |
| 8. | I was self-controlled. | 1 | 2 | 3 | 4 |
| 9. | I could concentrate easily. | 1 | 2 | 3 | 4 |
| 10. | I saved my money regularly. | 1 | 2 | 3 | 4 |
| 11. | I couldn't keep still at plays or lectures. | 1 | 2 | 3 | 4 |
| 12. | I was a careful thinker. | 1 | 2 | 3 | 4 |
| 13. | I planned my career. | 1 | 2 | 3 | 4 |
| 14. | I said things without thinking. | 1 | 2 | 3 | 4 |
| 15. | I liked to think about complex problems. | 1 | 2 | 3 | 4 |
| 16. | I changed interests or hobbies frequently. | 1 | 2 | 3 | 4 |
| 17. | I acted "on impulse." | 1 | 2 | 3 | 4 |
| 18. | I got easily bored when solving thought problems. | 1 | 2 | 3 | 4 |
| 19. | I acted on the spur of the moment. | 1 | 2 | 3 | 4 |
| 20. | I was a steady thinker. | 1 | 2 | 3 | 4 |
| 21. | I bought things on impulse. | 1 | 2 | 3 | 4 |
| 22. | I could only think about one thing at a time. | 1 | 2 | 3 | 4 |
| 23. | I spent or charged on credit more than I earned. | 1 | 2 | 3 | 4 |
| 24. | I often had unrelated thoughts while thinking. | 1 | 2 | 3 | 4 |
| 25. | I was more interested in the present than the future. | 1 | 2 | 3 | 4 |
| 26. | I was restless at the theater or lectures. | 1 | 2 | 3 | 4 |
| 27. | I liked puzzles. | 1 | 2 | 3 | 4 |
| 28. | I was future oriented. | 1 | 2 | 3 | 4 |

Directions: For each item, indicate how well the sentence describes what you were like as a teenager. Please be as accurate and honest as you can be. Respond to each item as if it were the only item. That is, don't worry about being "consistent" in your responses.

**When I was a teenager…**

| | | Not true for me | A little bit true for me | Quite true for me | Very true for me |
|---|---|---|---|---|---|
| 1. | A person's family was the most important thing in life. | 1 | 2 | 3 | 4 |
| 2. | Even if something bad was about to happen to me, I rarely experienced fear or nervousness. | 1 | 2 | 3 | 4 |
| 3. | I went out of my way to get things I want. | 1 | 2 | 3 | 4 |
| 4. | When I was doing well at something I loved to keep at it. | 1 | 2 | 3 | 4 |
| 5. | I was always willing to try something new if I thought it will be fun. | 1 | 2 | 3 | 4 |
| 6. | How I dressed was important to me. | 1 | 2 | 3 | 4 |
| 7. | When I got something I wanted, I felt excited and energized. | 1 | 2 | 3 | 4 |
| 8. | Criticism or scolding hurt me quite a bit. | 1 | 2 | 3 | 4 |
| 9. | When I wanted something I usually went all-out to get it. | 1 | 2 | 3 | 4 |
| 10. | I often did things for no other reason than that they might be fun. | 1 | 2 | 3 | 4 |
| 11. | It was hard for me to find the time to do things such as get a haircut. | 1 | 2 | 3 | 4 |
| 12. | If I saw a chance to get something I wanted, I moved on it right away. | 1 | 2 | 3 | 4 |
| 13. | I felt pretty worried or upset when I thought or knew somebody was angry at me. | 1 | 2 | 3 | 4 |
| 14. | When I saw an opportunity for something I liked, I got excited right away. | 1 | 2 | 3 | 4 |
| 15. | I often acted on the spur of the moment. | 1 | 2 | 3 | 4 |
| 16. | If I thought something unpleasant was going to happen I usually got pretty "worked up." | 1 | 2 | 3 | 4 |
| 17. | I often wondered why people acted the way they did. | 1 | 2 | 3 | 4 |
| 18. | When good things happened to me, it affected me strongly. | 1 | 2 | 3 | 4 |
| 19. | I felt worried when I thought I had done poorly at something important. | 1 | 2 | 3 | 4 |
| 20. | I craved excitement and new sensations. | 1 | 2 | 3 | 4 |
| 21. | When I went after something I used a "no holds barred" approach. | 1 | 2 | 3 | 4 |
| 22. | I had very few fears compared to my friends. | 1 | 2 | 3 | 4 |
| 23. | It excited me to win a contest. | 1 | 2 | 3 | 4 |
| 24. | I worried about making mistakes. | 1 | 2 | 3 | 4 |

Appendix 7.1

Article

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